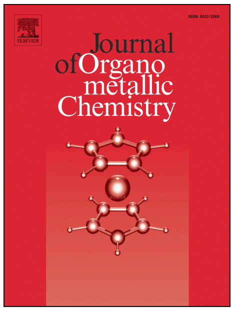


Cross-linked polystyrene/titanium tetrachloride as a tightly bound complex catalyzed the modified Mannich reaction for the synthesis of piperidin-4-ones

Ali Rahmatpour, Reza Emen, Ghazal Amini

PII: S0022-328X(19)30130-5
DOI: https://doi.org/10.1016/j.jorganchem.2019.04.004
Reference: JOM 20754

To appear in: *Journal of Organometallic Chemistry*

Received Date: 7 December 2018
Revised Date: 17 February 2019
Accepted Date: 5 April 2019

Please cite this article as: A. Rahmatpour, R. Emen, G. Amini, Cross-linked polystyrene/titanium tetrachloride as a tightly bound complex catalyzed the modified Mannich reaction for the synthesis of piperidin-4-ones, *Journal of Organometallic Chemistry* (2019), doi: https://doi.org/10.1016/j.jorganchem.2019.04.004.

Cross-linked polystyrene/titanium tetrachloride as a tightly bound complex catalyzed the modified Mannich reaction for the synthesis of piperidin-4-ones

Ali Rahmatpour[*], **Reza Emen, Ghazal Amini**

Polymer Research Laboratory, Faculty of Chemistry, Shahid Beheshti University, P. O. Box: 19839-4716, Tehran, Iran; Fax: +98 21 22431671; Tel: +98 21 29903250
**Corresponding author E-mail: a_rahmatpour@sbu.ac.ir*

Abstract

Cross-linked polystyrene beads were prepared, characterized and the resulting polymer carrier was functionalized with titanium tetrachloride ($TiCl_4$) via complexation of polystyrene with $TiCl_4$ to afford the corresponding cross-linked polystyrene-$TiCl_4$ stable complex (PSt/$TiCl_4$) in an one step reaction and characterized by FT-IR, UV, TGA, DSC, XRD, SEM, BET. This tightly bound coordination complex was used as a water tolerant, heterogeneous, recoverable and reusable Lewis acid catalyst for the synthesis of substituted piperidin-4-ones via the modified Mannich multi-component condensation of ketones, aromatic aldehydes, and ammonium acetate in 1:2:1 molar ratio under mild conditions. The rate of reactions was found to decrease with an increasing percentage of crosslinking and the mesh size of the copolymer beads. The catalyst is water tolerant, stable and can be easily recovered and reused at least four times without any loss of activity.

Keywords: Polymer/Lewis acid coordination complex, Polystyrene-supported catalyst, Substituted piperidin-4-one, Multi-component reaction

1. Introduction

Heterogeneous catalysis is a clean and environment-friendly catalytic method. The possibility of performing multicomponent reactions with a heterogeneous catalyst could enhance their efficiency from an economic as well as ecological point of view [1]. Although various catalysts have been developed to realize organic transformation under homogeneous conditions, it is still difficult to achieve recovery and reuse of the catalysts in many cases. Preparative procedures using polymer-supported catalysts have several advantages beacause of their nature; the most important properties of such catalysts are as active as their homogeneous counterparts while having the distinguishing characteristics of being easily separable from the reaction media, reusability, higher selectivity, enhanced stability, easier handling, non-toxicity, non-corrosiveness, and simple workup procedures [2,3].

Over the past few years, $TiCl_4$ has been reported as an efficient catalyst for organic synthesis and industrially organic compounds, which exhibits, in numerous cases, a stronger activity than other known metal chlorides, in particular those of transition elements [4–6]. Even though free $TiCl_4$ has many advantages in a homogeneous environment, it has drawbacks such as its corrosive nature, moisture sensitivity, less stability at room temperature, handling difficulty, a hazardous nature, and can not be recovered. Immobilized $TiCl_4$ catalyst is expected to solve these problems. The heterogenisation of inorganic reagents and catalysts in an inert matrix that are useful in organic reactions is an important goal in clean technology [7]. Polystyrene (frequently as a cross-linked resin) is one of the most popular polymer supports, due to its availability, facile functionalization and chemical inertness [8]. There are several different ways by which active homogeneous catalysts have been heterogenized for use in organic synthesis. Perhaps a most attractive method known to date is immobilization of active catalysts on an inert organic polymer matrix [8]. One of the interesting aspects of such immobilized catalysts is that they swell under certain solvent conditions and thus provide a near homogeneous environment for the reactants while retaining all the advantages of a heterogeneous catalysts. The aim of this study was to heterogenize and immobilize strong Lewis acid titanium tetrachloride directly by supporting it on cross-linked polystyrene with specified morphology in an one step reaction without functionalization of the polymer matrix.

We have recently reported the synthesis and use of polymer-supported Lewis acids as efficient catalysts for a variety of organic transformations [9-14]. Cross-linked polystyrene-supported titanium tetrachloride (PS/$TiCl_4$), which is a tightly bound and stable complex between $TiCl_4$ and polystyrene-divinylbenzene copolymer. The use of the PS-$TiCl_4$ complex catalyst has several advantages over a conventional acid catalyst, such as its ease of handling (as a bench-top catalyst), stability, cost efficiency, recyclability, and tunable Lewis acidity.

Nitrogen containing heterocyclic compound especially piperidin-4-ones presumably gaining considerable importance owing to their varied biological properties such as antiviral, antifungal, anti-tumour, analgesic activities [15-17]. Substituents (presence phenyl or *para* substituted phenyl groups) at C-2 and C-6 positions of the piperidin-4-one ring moiety have a wide range of antimicrobial activity.

Multicomponent reactions (MCRs) are chemical transformations in which three or more reactants form a product derived from all of the inputs in a single operation without isolating the intermediates and therefore reducing the reaction times and energy input [18-20]. These type of reactions introduce the most of diversity in one step, making full use of the many building blocks available today from commercial vendors. The interest in MCRs has boosted during the past two decades since are a very useful tool for the efficient synthesis of small molecule libraries. The search and discovery for new as well as improvement of known MCRs is still in demand as the best tools in combinatorial chemistry. One of these MCRs is the preparation of piperidin-4-one derivatives by a three-component reaction using ketones, aromatic aldehydes, and ammonium acetate (in 1:2:1 molar ratio) reported by Noller *etal.* [21]. A few number of methods are available for the synthesis of substituted piperidin-4-ones [22-27] and a few catalysts are also available up to now to improve the yield and reaction conditions of the modified Mannich reaction. The main disadvantage of almost all conventional methods is that the catalysts are destroyed in the work-up procedure and their recovery and reuse is often impossible, and most importantly, the conventional method of synthesis of polysubstituted piperidin-4-one derivatives necessitate a tedious work-up procedure, including the conversion of the product to its hydrochloride salt. Thus, the development of new methods that utilize eco-friendly protocols are highly desirable.

As part of our continuing interest in heterogeneous catalysis in organic transformations, we report herein an efficient and eco-friendly procedure for the synthesis of substituted piperidin-4-one derivatives from the modified Mannich condensation of ketones, aromatic aldehydes, and ammounium acetate catalyzed by a tightly bound DVB-PS/$TiCl_4$ complex as a reusable heterogeneous Lewis acid catalyst in ethanol for the first time (Scheme 1). In this study, the preparation of DVB-crosslinked PS-$TiCl_4$ complex by directly immobilization of $TiCl_4$ on PS with specified crosslinking degree, mesh size, and morphology prepared by carrying out cross-linking suspension copolymerization using xanthan gum/ or guar gum from bioresources as new alternative synthetic suspension stabilizer is also described. A tightly bound complex PS/$TiCl_4$ combines the advantages of being both a Lewis acid and a dehydrating agent.

<Scheme 1>

2. Experimental section

2.1. Preparation of cross-linked polystyrene copolymer beads

Into a 250 ml three-necked round-bottomed flask equipped with a mechanical stirrer, nitrogen gas inlet, and reflux condenser that is placed in a thermostated water bath, a mixture of distilled water (500 parts) containing GG or XG/PVA (2 wt% in relation to the monomers) and NaCl (1% w/v in relation to water volume) was first introduced into the flask and stirred at room temperature for 30 min. While stirring, nitrogen was purged from the mixture, the suspending medium was then heated to the reaction temperature. A mixture of the monomers (St and several weight ratios of DVB cross-linker, 4, 6, 8, 10%) were first mixed well with the porogen (toluene-heptane (3:2) mixture) to form an organic phase in which, the initiator, AIBN, was added in the amount of 1 mol% of monomers. The organic phase mixture was then added dropwise to the aqueous phase, through a dropping funnel to the flask for about 30 min (The volume ratio between the two phases (organic/aqueous) was kept constant at 1/5). The stirring rate was kept at 350-400 rpm and the polymerization was allowed to proceed at 80 ^{o}C for 18 h. After the polymerization, the copolymer beads were filtered out on a Buchner funnel under vacuum, and treated in 1N HCl at boiling temperature for 15 min, washed twice with hot water, and then vacuum filtered to remove the stabilizer. The copolymer beads were extracted thoroughly with acetone for a few hours in a soxhlet apparatus to remove porogen and residual monomers, and then were washed twice with acetone, two times with methanol to ensure complete removal of impurities. Finally, the samples were dried in a vacuum oven at 50 ^{o}C for at least 8 h. The overall conversion of the monomers to solid copolymer was determined gravimetrically. Of these beads the 50-80 mesh size (or 170-290 μm) beads were used in the subsequent studies.

2.2. Preparation of crosslinked polystyrene-titanium tetrachloride complex (PS/TiCl$_4$)

The carrier beads of cross-linked polystyrene (8% DVB, grain size range: (170-290 μm, 50-80 mesh size) swelled by 6 mL of dry carbon disulfide as the reaction medium were placed in a round bottom flask (100 mL) equipped with a condenser. A solution of anhydrous TiCl$_4$ (2 g) in dry carbon disulfide (4 mL) was added to the dispersed polystyrene bead solution. The mixture was kept under refluxing conditions and stirring using a magnetic stirrer for 1 h under a nitrogen atmosphere. After cooling the reaction mixture to room temperature, cold water (50 mL) was then cautiously added to hydrolyze the uncomplexed TiCl$_{4.}$ The mixture was stirred until the bright red color disappeared, and the polymer became light yellow. The polymer beads were collected by filtration through suction and washed thoroughly with water (100 mL) and then with ether (10 mL) and chloroform (10 mL), respectively. The light yellow colored complex catalyst sample was further dried in a vacuum oven overnight at 50 ^{o}C before use. The chlorine content of PS/$TiCl_4$ was 11.62 % analyzed by the Mohr titration method [9-11] and the loading capacity of $TiCl_4$ on the polymeric catalyst or the amount of $TiCl_4$ complexed with polystyrene was calculated to be 0.824 mmol/g complex bead [28].

2.3. Determination of the quantity of $TiCl_4$ complexed

The PS-$TiCl_4$ complex samples were decomposed by burning via the sodium fusion method. The amount of $TiCl_4$ complexed with polystyrene carrier was calculated from the chlorine content. The chlorine content was determined volumetrically. It was also determined by the inductively coupled plasma (ICP) spectroscopy technique from the titanium content.

2.4. Determination of acidity (pH) of the PS-$TiCl_4$ complex

The catalyst sample was hydrolyzed in an acetone-water solution (60%, 3/2 v/v) at room temperature. The pH of the resultant solution was determined at 25 ^{o}C by using a standard pH meter.

2.5. General procedure for the one-pot synthesis of 3,5-dialkyl-2,6-diarylpiperidin-4-ones **4**

A mixture of benzaldehyde (2 mmol), ammonium acetate (1 mmol), ketones (1 mmol) and the PS/$TiCl_4$ containing certain amount of $TiCl_4$ (0.15 gr, 0.1 mmol of $TiCl_4$) in anhydrous ethanol (8 mL) was heated at 70 ^{o}C for an appropriate time as indicated by TLC (Table 2). After completion of the reaction, the mixture was cooled to room temperature and the resulting mixture was filtered to recover the catalyst and the filtrate was evaporated off the solvent to afford the crude product. The recovered catalyst was washed by ethanol, ether, and dried at 60 ^{o}C for 6 h and stored in a desiccator. The crude product obtained was washed with water and purified by recystallization from ethanol and ethanol-acetone (3:2, v/v) to afford the corresponding pure compound. 10 mmol-scale reactions were also carried out without any difficulties. All of the known products were characterized by comparison of their physical data, FTIR, and ^{1}H NMR spectra with those of authentic samples.

3. Results and discussion

3.1. Synthesis and characterization of crosslinked poly (St-DVB) beads and their titanium tetrachloride complex

The polymeric carrier beads as polymer support were synthesized by aqueous cross-linking suspension radical copolymerization of styrene-divinylbenzene (with varying ratios of DVB) monomers using guar or xanthan gum as a biopolymer suspension stabilizer in the presence of AIBN and non reactive diluents (Scheme 2). The present study deals with using the copolymer beads containing (8 wt.%) of DVB as cross-linker as the polymer carrier beacause of the network consisting of light and relatively larger number of accessible domains leading to higher functionalization. All resins were sieved to a range of 25-80 mesh. The 50-80 mesh beads were used as carrier in the polymer supported catalysts.

The cross-linked polystyrene analog of ethylbenzene-$TiCl_4$ complex was synthesized by complexation reaction of the PS with $TiCl_4$ in an one step reaction without functionalization of the polymer matrix. The steps involved in the preparation of DVB/PS-supported titanium tetrachloride are given in Scheme 2. The complex formation takes place via the formation of a coordination bond between the $TiCl_4$ and the PS carrier. Since titanium in $TiCl_4$ has the vacant d-orbital (d^0) so it has the ability to accept the π electron donated from the electron rich PS moiety leading to a PS-$TiCl_4$ complex.

<Scheme 2 >

In order to ascertain the incorporation of $TiCl_4$ to the polymer support, FT-IR spectra were recorded separately at different satges of synthesis (Fig. S1, see supplemenrtary data). Comparison of the IR spectra of the PS carrier and the supported catalyst PS/$TiCl_4$ revealed that the peak intensity centered at 3025 cm^{-1} (=CH- stretching of benzene ring) significantly decreases, indicating a reduction in the electron density on the carbon-carbon (π) double conjugated bond. This is due to the donation of electron density from π bond to the vacant d orbital of Ti^{+4} in $TiCl_4$. The main difference between the FT-IR spectra of PS/$TiCl_4$ complex and crosslinked PS was at 1500-1600 cm^{-1} and at 500-800 cm^{-1}. The FT-IR spectrum of PS/$TiCl_4$ showed new peaks at 1500-1590 cm^{-1} due to for C-C stretching, 500-800 cm^{-1} for benzene ring C-H bending, indicating the donor-acceptor interaction of carbon-carbon (π) bond on the benzene rings with $TiCl_4$. This interaction causes weakening carbon-carbon bond and this characteristic absorption band (C-C stretching) negatively shifts to 1540 cm^{-1}, indicating coordination of the π bond with the titanium and further confirming the formation of a titanium complex on the surface of the polymer and modification of the phenyl rings of the PS/DVB.

The FT-IR spectra of pyridine adsorbed on PS/$TiCl_4$ Lewis acid and PS samples are shown in Fig. S2. After adsorption of pyridine, the characteristic absorption band at 1450 cm^{-1} is originated C-C stretching vibration in pyridine molecules coordinatively chemisorbed on Lewis sites (Ti), so it was attributed to Lewis acid sites. The other signals for pyridine molecules coordinatively chemisorbed on Lewis sites are about 1493 and 1600 cm^{-1} (C-C ring vibration). However, no band at the same wavelength was observed for the PS sample. Therefore, it was proved that the Lewis acids were successfully immobilized on polystyrene.

The UV spectrum of the solution of PS/$TiCl_4$ complex in CS_2 showed a new absorption band at about 262 nm, which is due to the formation of a stable Pi→P type coordination complex between the benzene rings in the polystyrene carrier with $TiCl_4$. This effect would also stabilize the $TiCl_4$ complex with polymer carrier containing phenyl groups. UV spectra of PS, PS/$TiCl_4$ are shown in Figure S2. The probable way of complex formation is shown in Scheme S1 (see supplementary data). As a result of the electron donation from PS moiety to $TiCl_4$, the Lewis acid is stabilized due to the decreased mobility of the benzene rings hindered by the long polystyrene chain. These significant changes revealed that $TiCl_4$ is coordinated with benzene rings through the π bond. The white polystyrene beads becomes pale yellow after the heterogenation with $TiCl_4$ which gives physical evidence of complex formation taking place between $TiCl_4$ and polystyrene beads.

The pH of PS-$TiCl_4$ complex catalyst dispersed in a solution of acetone-water (60%) is shown in Fig. S4 (see supplementary data). Figure S4 shows that the acidity due to hydrolysis of this polymeric complex in solution increases with time and reached equilibrium in 2 h. This is due to the liberation of HCl into the acetone-water solution after reaction of $TiCl_4$ incorporated in PS with water. This confirms that some Lewis acid ($TiCl_4$) is present in this polymeric complex. The same experiment was also performed with the naked polymer which shows pH= 6.2 (Fig. S4).

Fig. S5 shows the XRD diffraction pattern of the PS carrier and the synthesized PS/$TiCl_4$ catalyst (see supplementary data). The virgin PS exhibited a broad diffraction peak at (2θ) ranging from 15^o-30^o suggesting the amorphous structure of the polymeric scaffold (see supplementary information). But in case of PS/$TiCl_4$ after incorporation of $TiCl_4$ into the polymer matrix, the intensity of characteristic reflection peak at $2\theta=15^o$-30^o has been considerably diminished without altering the peak position. The reason for the decrease in peak intensity is probably due to the accommodation of $TiCl_4$ molecules onto the PS matrix which combine the polymer chain and it forms complexes with polystyrene. This phenomenon confirms the presence of $TiCl_4$ in the polystyrene matrix.

The incorporating of $TiCl_4$ in PS carrier was also confirmed by using TGA technique. Fig. 1 presents the thermal behavior of the PS and the as-synthesized PS-supported catalyst. The PS bead showed single step degradation. The initial decomposition temperature of the PS was occurred at about 334 ^oC. The major degradation of the polymer chain occurs in the range of 380-440 ^oC (midpoint 422.38 ^oC) and the loss is related to breaking the main chain and side group of PS. But in case of $TiCl_4$ incorporated PS catalyst, the weight loss starts at about 50 ^oC. This weight loss could be assigned to the release of residual solvent and adsorbed water. Except the slightly initial weight loss, the synthesized PS/$TiCl_4$ showed one step degradation. The major degradation of the polymer chain occurs in the range of 310-450 ^oC (50 % weight loss at about 417 ^oC and (80% weight loss at about 450 ^oC). The degradation temperature (2nd) slightly decreases with the incorporation of $TiCl_4$ into the polymer matrix. The lower second degradation temperture of catalyst relative to that of the pristine polystyrene is mainly due to loss of crystallinity of PS by incorporation of $TiCl_4$ and to an outlet of $TiCl_4$ from the polystyrene matrix. The TGA data reveals that PS/$TiCl_4$ catalyst is thermally stable up to 210-270 ^oC (depending on percent of $TiCl_4$ loading), and so it may be inferred that this synthesized catalyst is sufficiently thermally stable to be applied for a variety of chemical transformations which is carried out in that temperature range including the modified Mannich condensation.

<Figure 1>

The DSC analysis provide analogous information (Figure 2). The maximum decomposition temperature (50 wt.% weight loss) for the copolymer bead prepared is about 402 ^oC. The glass transition temperature (T_g) of the copolymer beads (PS/DVB) with 4 and 8 wt.% DVB is about 108 and 119 ^oC, respectively. No exothermic peak in the range 200-250 ^oC was observed. For this peak, polymer cross-linking is responsible. Absence of such peaks in the case of copolymer beads prepared indicates that all double bonds of monomers were consumed during copolymerization.

<Figure 2>

SEM imaging provides more accurate information on the particle size and morphology of the polymer support and functionalized polymer carrier. Fig. 3 shows the SEM images of the PS carrier and the sample after immobilization. A clear change in morphology was observed after incorporating $TiCl_4$ onto the polymer support. It can be seen from Fig. (3a) that the PS carrier exhibits randomly regular shape particles and almost non uniform in their sizes with an average diameter of 500 μm. The SEM image shown in Fig.(3b) after incorporation of $TiCl_4$ on the polymer matrix, randomly irregular aggreagated particles are observed. Moreover, it was observed that the particle size becomes considerably larger than the pristine one and the surface becomes slender smooth. The observed increase in particle diameter of the catalyst particle could be a further evidence of an effective incorporating of $TiCl_4$ with the polymer. The above result is a clear indication of the chemical immobilization of the active catalyst on the support of PS.

<Figure 3>

The loading capacity of the polymeric catalyst based on its chloride content obtained by gravimetric method and checked by atomic absorption technique was 0.824 mmol $TiCl_4$/g of complex catalyst beads [27]. The data obtained by these two techniques showed, within experimental error, that the catalyzing species are in the form of $TiCl_4$ supported on the polymeric support.

To verify the incorporation of $TiCl_4$ Lewis acid onto polystyrene, the corresponding structural parameters such as surface area and total pore volumes of PS and PS/$TiCl_4$ were caculated with the Brunauer-Emmet-Teller (BET) method. In Table S1, porous structure parameters of the studied PS and PS/$TiCl_4$, and catalyst loading of PS/$TiCl_4$ are presented. As BET surface area of PS carrier bead is almost totally contributed by its open pore system, the catalytic functional group prepared via this scheme should have been evenly confined in the pores. BET surface area measurements indicated that, after immobilization, the BET surface area of PS decreased from 42 to 12.24 m^2/g and pore volume decreased from 0.14 to 0.035 ml/g which was attributed to the surface functionalization in the PS support (the loading of $TiCl_4$ in the pores). The reduction of both surface area and pore volume of the catalyst compared to the original PS support confirms the presence of Lewis acid moieties within the pores of the support. The structure of the parent material (polymer chain) was unaffected after this step; however, a decrease in the PS surface area, as well as some blockage of pores and a slight decrease in the mean pore size are observed, as expected (Table S1, supplementary data).

*3. 2. Catalytic activity of the PS/$TiCl_4$ complex on synthesis of polysubstituted piperidin-4-ones **4***

Among a number of metal chlorides used in organic synthesis, anhydrous titanium tetrachloride is undoubtedly one of the most effective and strong Lewis acid catalysts and shows unique reactivity in various organic and polymerization reactions [29]. However, it is found to be highly toxic, corrosive, and moisture sensitive, and so its usage, storage, and separation from the reaction mixture were invariably difficult; the strictly anhydrous conditions and stoichiometric amounts or more are required in order to achieve good yields. Moreover, several molar equivalents of triethylamine to titanium tetrachloride are also needed to improve the reaction yields [30,31]. Therefore, this study aimed at developing a non-toxic, low cost, environmental-friendly, readily available heterogeneous catalyst with high activity, simple preparation and capable of reuse by incorporation of $TiCl_4$ on the organic PS support. The resulting polymer protected reagent, a stable tightly bound complex between anhydrous $TiCl_4$ and PS-DVB copolymer beads was used for one-pot, three-component synthesis of polyfunctionalized piperidin-4-one compounds via a modified Mannich type reaction. The complex of the polymer and $TiCl_4$ provides a shelf-stable acidic, water tolerant material and it is not easily hydrolyzed by water.

To examine the catalytic behaviour of PS/$TiCl_4$ complex and find the optimum conditions in the three-component modified Mannich condensation, the reaction of benzaldehyde (2 mmol), ammonium acetate (1 mmol), and butan-2-one (1 mmol) was chosen as a model. The effects of temperature, catalyst concentration, reaction media, and reaction time were investigated and the results were summarized in Table 1. The initial reaction was carried out using 10 mol% of PS/$TiCl_4$ complex in ethanol at room temperature (Table 1, entry 10). The reaction yield was 36% after 6 h and increased with increasing temperature. The reaction temperature has a great influence on the model reaction. The reactions were carried out in ethanol at different temperatures ranging from 30 to 70 ^{o}C. It is clear that at lower temperatures, even if the time was prolonged to 8 h, only low yields were obtained (Table 1, entries 10-12). The optimal temperature was found to be 70 ^{o}C with a 93% yield. The reason for requiring a higher temperature was probably due to the weaker acidity of PS/$TiCl_4$ compared to anhydrous $TiCl_4$. In addition, microporous pores and channels of polystyrene were unfavorable for the molecular mass transfer process. Next, we examined the effect of the amount of catalyst on the reaction and it was found that the catalyst dosage was also an important factor for the reaction, as 8 mol% of PS-$TiCl_4$ gave a yield of 82% after 4 h while 10 mol% of PS-$TiCl_4$ was sufficient to give the yield of 93% after 1 h. A control experiment was conducted in the absence of PS-$TiCl_4$. This afforded the desired product **4a** in only 34 % yield after 16 h (Table 1, entry 7) and necessitate a tedious work-up procedure, including the conversion of the product to its hydrochloride salt, performed according to the conventional method in literature [20], but on adding 5 and 8 mol% catalyst to the system under similar conditions the rate of reaction was obviously accelerated, but the yields were unsatisfactory. Increasing the amount to 10 mol% not only increased the yield but also shortened the reaction time (Table 1, entries 8,9,11).

The choice of the solvent appeared crucial in order to maximize yield. Among the various solvents surveyed, the highest yield was obtained in C_2H_5OH (Table 1, entries 1-5,12). The highest yield obtained by using C_2H_5OH as the solvent can be ascribed to the fruitful swelling of the polymer network of the catalyst and miscibility with the substrates in this media, allowing the metal particles located inside the polymer matrix to effect the catalysis. No reaction occurred when H_2O was used as solvent, may be because of aggregation of the catalyst, caused by its hydrophobic nature, led to inadequate access of the substrates to the active sites of the catalyst (Table 1, entry 6). Among the various solvents tested, ethanol serve to swell the polymer and make the titanium chloride more accessible. To confirm the activity of PS-$TiCl_4$ complex, a comparison experiment was carried out by using PS carrier alone under the same experimental conditions, the desired adduct product in 34% yield was isolated (Table 1, entry 13). This indicated that the PS itself did not promote the reaction and the catalytic activity arises from the Lewis acid $TiCl_4$ moiety of the polystyrene-supported catalyst. Also, PS/$TiCl_4$ was found to be a more effective catalyst than PS/$AlCl_3$ for the synthesis of **4a** under identical conditions (Table 1, entry 16). In order to compare the catalytic activity of the homogeneous phase and heterogeneous phase at the same reaction conditions and to clarify the role of the carrier PS, we have performed the catalytic model reaction in the presence of the corresponding soluble monomer analog, ethylbenzene-$TiCl_4$ complex as the homogeneous phase in C_2H_5OH at the same conditions (Table 1, entry 14) and the homogeneous complex afforded **4a** in 82% yield. The surface area is absent in the homogeneous catalyst of ethylbenzene-$TiCl_4$. Thus, the yield of the condensation product over PS/$TiCl_4$ is much higher than the homogeneous complex catalyst. We have also performed the model reaction in the presence of $TiCl_4$ as the homogeneous phase at the same experimental conditions and afforded the sticky undesired product (Table 1, entry 17). This data clearly suggests that the microporous polystyrene as support plays a crucial role in this condensation reaction. The more efficient accessibility of the reactants to the catalyst's active sites is probably the main reason for the improvement in the yield compared to $TiCl_4$. On complexation of PS support with $TiCl_4$, it is stabilized due to the decreased mobility of the benzene rings hindered by the long polystyrene chain and no need the several equivalents of organic base such as, triethylamine to stabilize $TiCl_4$ and the improve of reaction yields [29,30]. Thus, the yield of the condensation product over our reusable and heterogeneous polystyrene-supported $TiCl_4$ is much higher than the homogeneous $TiCl_4$ free form and also could be avoid tedious extra wok-up after completion of the reaction and reduce the amount of acidic waste water generated.

To realize whether the reaction occurred in the solid matrix of the supported catalyst or whether $TiCl_4$ simply released into the ethanol was responsible for the reaction, catalyst PS/$TiCl_4$ was stirred in ethanol for 20 min and then isolated by filtration. When the reactants were added to the filtrate and stirred for 2.5 h, gave a low yield 35 % (Table 1, entry 15). These results indicated the reaction takes place in the solid matrix and that release of $TiCl_4$ is negligible. Moreover, To rule out the presence of concurrent homogeneous catalysis, the model reaction was carried out in the presence of the PS/$TiCl_4$ catalyst until the conversion was about 50 % (30 min) and at that point the catalyst was removed by filtration. Further treatment of the filtrate under similar reaction condition did not proceed significantly (Table 1, entry 18). Additionally, the ethanol-treated PS/$TiCl_4$ catalyst was used for the synthesis of **4a** under identical conditions. It was observed that the yield of desired product was almost the same as its yield by using the pristine PS/$TiCl_4$ (Table 1, entry 19).

<Table 1>

To check the reusability of the catalyst, the model reaction to provide **4a** under the conditions described was run for four consecutive cycles, furnishing the corresponding product in 93, 92, 89, 87% isolated yields, which proved the efficiency of the catalyst for multiple usage (Table 2). Even though after four consecutive cycles run for the reaction, the catalytic activity of PS/$TiCl_4$ did not decrease dramatically. The gradual decrease in catalytic activity may be due to blocking of some active sites on the catalyst surface by the residues of the reaction. Furthermore, there were no significant differences between the IR spectra of the initial and spent catalyst, which may indicate there was no degradation of the supported catalyst. The extent of titanium ion leaching from the catalyst was very low (<14-16 ppm) as judged by ICP analysis.

<Table 2>

Encouraged by the results described above, the one-pot condensation of substituted piperidin-4-ones **4** catalyzed by PS/$TiCl_4$ complex catalyst was extended to other aromatic aldehydes and ketones to explore the scope of this procedure. The results are summarized in Table 3. Accordingly, a variety of substrates were submitted to the optimum reaction conditions, and the desired products were obtained in high yields. As can be seen from the results in Table 3, aromatic aldehydes containing both electron-withdrawing and electron-donating groups reacted smoothly with butan-2-one, pentan-2-one, and pentan-3-one to produce high yields of products. The yields obtained were good to excellent without the formation of any side products. We observed, irrespective, of groups on the aromatic ring, that the reaction time and yields are almost close to each other.

<Table 3>

4. Conclusion

The polymer carriers, DVB-PS copolymers were synthesized by aqueous cross-linking suspension radical copolymerization of styrene-divinylbenzene (with varying ratios of DVB) monomers using biopolymers as a suspension stabilizer and the polymer-supported $TiCl_4$ catalyst was prepared by complexation of PS with $TiCl_4$ in an one step reaction without functionalization of the polymer matrix. PS/$TiCl_4$ was shown to be an efficient and recyclable catalyst for the modified Mannich condensation reaction of ketones, aromatic aldehydes, and ammonium acetate. The advantage of this approach is to prepare catalyst displaying good activity, selectivity, and reproducibility typical of homogeneous catalysts, combined with the easy separability and recovery characteristics of heterogeneous catalysts.

Acknowledgements

The authors are thankful to TPC for providing the required chemicals and the Shahid Beheshti University Research Council for partial support of this work.

References

[1] M. Climent, A. Corma, S. Iborra, Homogeneous and heterogeneous catalysts for multicomponent reactions, RSC Adv. 2 (2012) 16–58.

[2] A. Akelah, The use of functionalized polymers as polymeric reagents and in solid phase organic synthesis, a review, React. Polym. 8 (1988) 273-284.

[3] Nicholas E. Leadbeater, M. Marco**,** Preparation of polymer-supported ligands and metal complexes for use in catalysis, Chem. Rev., 102 (10) (2002) 3217–3274.

[4] N. Ahmed, G. K. Pathe, S. Jheeta, $SnCl_4$ or $TiCl_4$: highly efficient catalysts for the detetrahydro pyranylation and demethoxymethylation of phenolic ethers and sequential one-pot asymmetric

synthesis of 3-aryl-2-hydroxy-2,3-dihydroindan-1-ones from chalcone epoxides, R SC Adv., 5 (2015) 63095-63103.

[5] H. Valizadeha, A. Shockravi, An efficient procedure for the synthesis of coumarin derivatives using $TiCl_4$ as catalyst under solvent-free conditions, Tetrahedron Lett. 46 (2005) 3501–3503.

[6] G. Xu, D. Cheng, Syndiospecific polymerization of styrene with half-sandwich titanocene catalysts. Influence of ligand pattern on polymerization behavior, Macromolecules 33 (2000) 2825-2831.

[7] A. Corma, H. Garcı´a, Lewis acids: From conventional homogeneous to green homogeneous and heterogeneous catalysis, Chem. Rev. 103 (2003) 4307−4365.

[8] C. A. McNamara, M. J. Dixon, M. Bradley**,** Recoverable catalysts and reagents using recyclable polystyrene-based supports, Chem. Rev. 102 (2002) 3717–3756.

[9] A. Rahmatpour, N.Goodarzi, M. Moazzez, A novel route for synthesis of cross-linked polystyrene copolymer beads with tunable porosity using guar and xanthan gums from bioresources as alternative synthetic suspension stabilizers, Designed Monomer Polym. 21(1) (2018) 116-129.

[10] A. Rahmatpour, Polystyrene-supported $AlCl_3$ as a highly active and reusable heterogeneous lewis acid catalyst for the one-pot synthesis of quinoxalines, Heteroat. Chem. 23(5) (2012) 472-477.

[11] A. Rahmatpour, One-pot synthesis of *N*-substituted pyrroles catalyzed by polystyrene-supported aluminum trichloride as a reusable heterogeneous lewis acid catalyst, Heteroat. Chem. 22(1) (2011) 85-90.

[12] A. Rahmatpour, Polystyrene-supported gallium trichloride: A new, highly efficient and recyclable heterogeneous Lewis acid catalyst for tetrahydropyranylation of alcohols and phenols**,** Polyhedron 44 (2012) 66-71.

[13] A. Rahmatpour, Polystyrene-supported gallium trichloride as a highly efficient and recyclable heterogeneous Lewis acid catalyst for one-pot synthesis of *N*-substituted pyrroles, J. Organom. Chem. 712 (2012) 15-19.

[14] A. Rahmatpour, S. Mohammadian, Polystyrene-supported titanium tetrachloride as a novel, efficient and reusable polymeric Lewis acid catalyst for the chemoselective synthesis and deprotection of 1,1-diacetates under eco-friendly conditions, Comptes Rendus Chimie 16 (2013) 912-919.

[15] P. Parthiban, G. Aridoss, P. Rathika, V. Ramkumar, S. Kabilan, Synthesis, spectral, crystal and antimicrobial studies of biological potent oxime ethers of nitrogen, oxygen and sulphur heterocycles, Biorg. Med. Chem. Lett. 19 (2009) 2981-2985.

[16] G. Aridoss, P. Parthiban, R. Ramachandran, M. Prakash, S. Kabilan, Y. T. Jeong, Synthesis and spectral characterization of a new class of N-(N-methylpiperazinoacetyl)-2,6-diaryl piperidin-4-ones: Antimicrobial, analgesic and antipyretic studies, Eur. J. Med. Chem. 44 (2009) 577-592.

[17] C. Ramalingan, Y. T. Park, S. Kabilan, Synthesis, stereochemistry and antimicrobial evaluation of substituted piperidin-4-one oxime ethers, Eur. J. Med. Chem. 41 (2006) 683-696.

[18] L. Weber, Multi-component reactions and evolutionary chemistry, Combinatorial Chem. 7 (2002) 143-147.

[19] Răzvan C. Cioc, E. Ruijter, Romano V. A. Orru, Multicomponent reactions: advanced tools for sustainable organic synthesis, Green Chem. 16 (2014) 1958-2975.

[20] James E. Biggs-Houck, A. Younai, Jared T. Shaw, Recent advances in multicomponent

reactions for diversity-oriented synthesis, Current Opinion in Chem. Biology, 14 (2010) 371-382.

[21] C. R. Noller,V. Balia, The preparation of some piperidine derivatives by the Mannich reaction, 70 (1948) 3853-3855.

[22] M. Srinivasan, S. Perumal, S. Selvaraj, (L)-Proline catalysed efficient synthesis of 3-substituted 2,6-diarylpiperidin-4-ones, Arkivoc (2005) (xi) 201-208.

[23] N. Nalini, C. Theivarasu, Synthesis and characterization of substituted piperdin-4-ones with dichloro(Cyclooctadiene) palladium(II). Chem. Sci. Transactions 3(2) (2014) 717-721.

[24] K. K. Goel, A. N. M. Goel, A. Gajbhiye, Synthesis and antimicrobial activity of piperidin-4-one derivatives, Biomed. Pharma. J. 1(1) (2008) 201-206.

[25] U. I. Mishah, M. U. Hasan, M. Arab, K. Pandiarajan, R. Sekar, Conformational analysis and ^{13}CNMR spectra of some 2,6-diarylpiperidin-4-ones. Magnetic Resonance Chem. 23 (1985) 291-295.

[26] S. D. Dindulkar, P. Parthiban, Y. T. Jeong, Boron trifluoride/SiO_2 is a simple and efficient Lewis acid catalyst for the one-pot synthesis of polyfunctionalized piperidin-4-ones, Monatsh Chem. 143 (2012) 113-118.

[27] Rastogi, S.; Rastogi, H. An efficient synthesis of some substituted piperidine-4-one thiosemicarbazone derivatives as potential anti convulsant under microwave irradiation. Indian J. Chem. 49 (2010) 547-553.

[28] P. Deshmukh, K. J. Padiya, M. M. Salunkhe, Friedel–Crafts acylation reaction using polymer supported aluminium chloride, J. Chem. Res. (S) **1999**, 9, 568-569.

[29] T. Mukaiyama, Titanium tetrachloride in organic synthesis [New synthetic methods], Angew. Chem. Int. Ed. Engl. 16 (1977) 817-826.

[30] A. Renzetti, E. Dardennes, A. Fontana, P. De Maria, J. Sapi, and S. Gerard, $TiCl_4$/Et_3N-promoted three-component condensation between aromatic heterocycles, aldehydes, and active methylene compounds, J. Org. Chem. 73 (2008) 6824–6827.

[31] A. Marrone, A. Renzetti, P. De Maria, S. Gerard, J. Sapi, A. Fontana, and N. Re, condensation of β-diester titanium enolates with carbonyl substrates: A combined DFT and experimental investigation, Chem. A Eur. J. 15 (2009) 11537-11550.

Figures/Schemes captions

Scheme 1 Synthesis of substituted piperidin-4-one derivatives catalyzed by PS/$TiCl_4$ complex

Scheme 2 Synthesis of polymeric carrier and its titanium tetrachloride complex

Figure 1 TGA thermograph of DVB-crosslinked PS carrier (up) and PS/$TiCl_4$ complex catalyst (down)

Figure 2. DSC thermograph of the copolymer beads (PS/DVB) with 4 and 8 wt.% DVB (top and bottom, respectively)

Figure 3. SEM images of PS carrier (up), PS/$TiCl_4$ (down) samples

Tables file

Table 1
Optimization of the PS/$TiCl_4$ complex-catalyzed one-pot reaction of ammonium acetate, benzaldehyde, and butan-2-one.[a]

Entry	Solvent	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	Toluene	10	8	32
2	THF	10	8	48
3	$CHCl_3$	10	8	45
4	DMF	10	8	56
5	CH_3CN	10	8	55
6	H_2O	10	8	NR[d]
7[c]	C_2H_5OH	-	16	34
8	C_2H_5OH	5	8	61
9	C_2H_5OH	8	4	82
10[e]	C_2H_5OH	10	8	41
11[f]	C_2H_5OH	10	5	81
12[g]	C_2H_5OH	10	1	93
13[h]	C_2H_5OH	-	8	34
14[i]	C_2H_5OH	-	2.5	82
15[j]	C_2H_5OH	10	20 min	35
16[k]	C_2H_5OH	10	3	80
17[l]	C_2H_5OH	10	2	83
18[m]	C_2H_5OH	10	0.5	69
19[n]	C_2H_5OH	10	1	92

[a] Reaction conditions: benzaldehyde (2 mmol), ammonium acetate(1 mmol), 2-butanone (1 mmol), solvent (6 mL), room temperature (refers here to 30 °C). [b] Isolated yield. [c] No catalyst.
[d] NR: No reaction. [e,f,g] The reactions were conducted at r.t., 60 and 70 °C, respectively.
[h] PS was used as catalyst. [i] The ethylbenzene-$TiCl_4$ complex was used as catalyst.
[j] Catalyst was stirred in ethanol and filtered after 20 min. [k] PS/$AlCl_3$ (capacity: 0.47 mmol/g) was used as catalyst. [l] $TiCl_4$ was used as catalyst. [m] Catalyst was filtered after 30 min. [n] Ethanol-treated PS/$TiCl_4$ (refluxing in ethanol for 1 h) was used as catalyst.

Table 2

Recycling potential of the PS/$TiCl_4$ for the synthesis of **4a**.[a]

No of cycles	Fresh	Run 1	Run 2	Run 3	Run 4	Run 5
Yield[b](%)	93	92	89	87	87	85
Time (h)	1	1	1	1.4	2	2.5

[a] *Reaction conditions*: benzaldehyde (2 mmol), ammonium acetate (1 mmol), butan-2-one (1 mmol), 70 °C, catalyst (10 mol%).

[b] Isolated yield of pure product.

Table 3

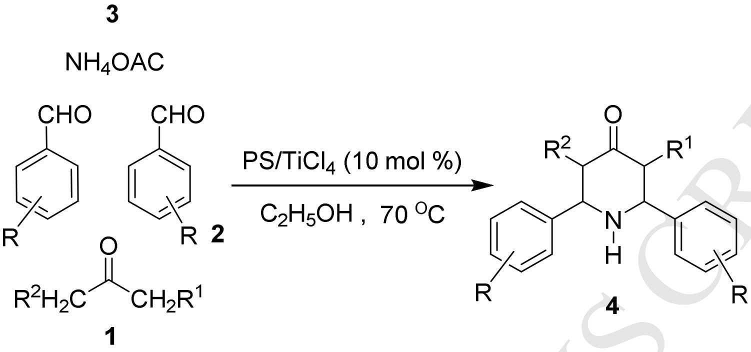
PS/$TiCl_4$- catalyzed synthesis of 3,5-dialkyl-2,6-diarylpiperidin-4-one derivatives **4**.

Entry	R	R^1	R^2	Product	Time (h)	Yield[c](%)	mp (°C) Ref.
1	H	CH_3	H	**4a**	1	93	86-87[21]
2	4-OCH_3	CH_3	H	**4b**	2	92	138-139[22]
3	4-Br	CH_3	H	**4c**	2.5	88	114-116[26]
4	4-CH_3	CH_3	H	**4d**	2.5	90	125-126 [22]
5	H	C_2H_5	H	**4e**	1	92	110-111[26]
6	4-Br	C_2H_5	H	**4f**	2	86	98-100 [26]
7	4-Cl	C_2H_5	H	**4g**	1.5	92	111-113[26]
8	4-$CH(CH_3)_2$	C_2H_5	H	**4h**	2	88	52-54 [26]
9	H	CH_3	CH_3	**4i**	1.5	86	133-134[21]
10	4-$CH(CH_3)_2$	CH_3	CH_3	**4j**	2	84	79-80 [26]
11	4-OCH_3	CH_3	CH_3	**4k**	2	91	140-142[21]
12	4-CH_3	CH_3	CH_3	**4l**	1.5	91	148- 150[21]
13	3-OCH_3	CH_3	H	**4m**	3	87	95-97[22,26]
14	3-OCH_3	C_2H_5	H	**4n**	3	86	77-79[22,26]
15[d]	d	CH_3	H	**4o**	2.5	89	193-194

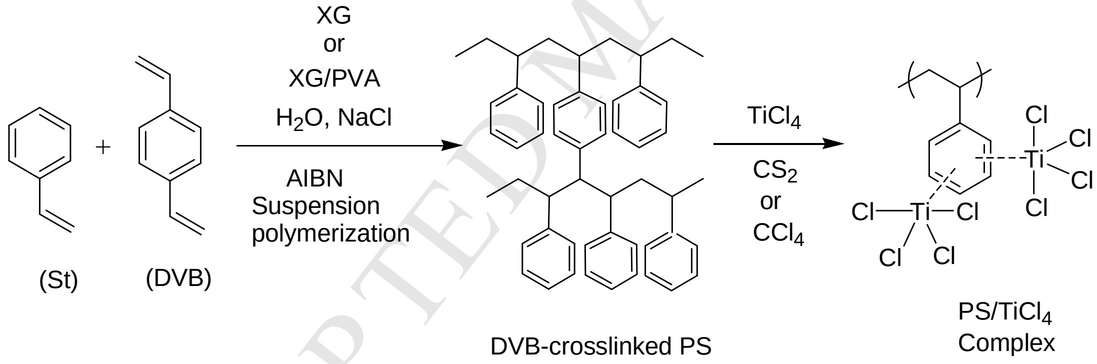
[a] *Reaction conditions*: All reactions were conducted with aromatic aldehydes (**2**, 2 mmol), ammonium acetate (**3**, 1 mmol), ketone (**1**, 1 mmole) using PS/$TiCl_4$ (10 mol%) in ethanol (6 mL) at 70 °C.

[b] All of the known products were characterized by comparison of their melting points, IR, and ^1H NMR spectra with those of authentic samples.[c] Yields refer to the isolated products. [d] 1-naphthaldehyde was used.

Schemes / Figures file



Scheme 1 Synthesis of substituted piperidin-4-one derivatives catalyzed by PS/$TiCl_4$ complex



Scheme 2 Synthesis of polymeric carrier and its titanium tetrachloride complex

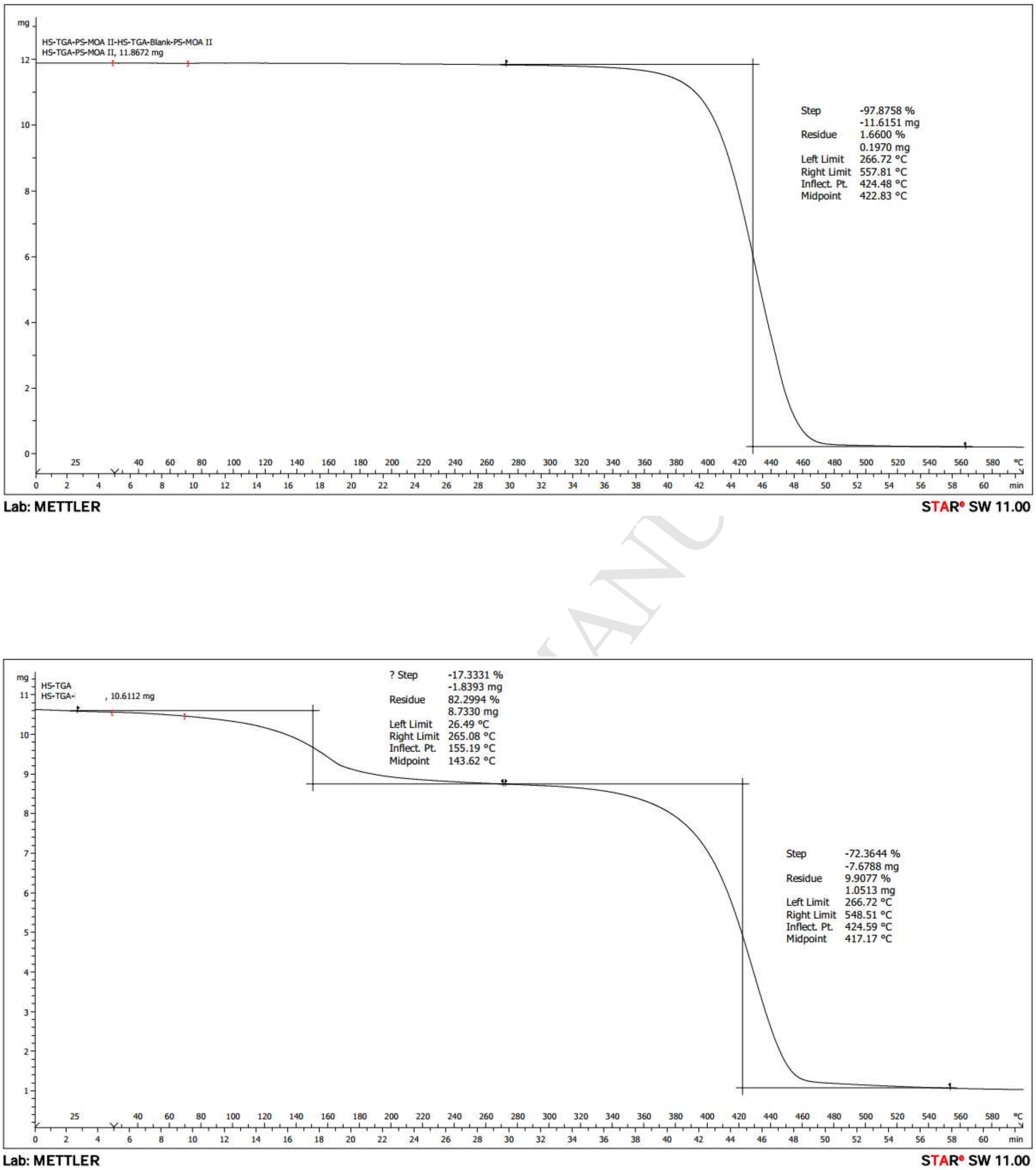


Figure 1 TGA thermograph of DVB-crosslinked PS carrier (up) and PS/$TiCl_4$ complex catalyst (down)

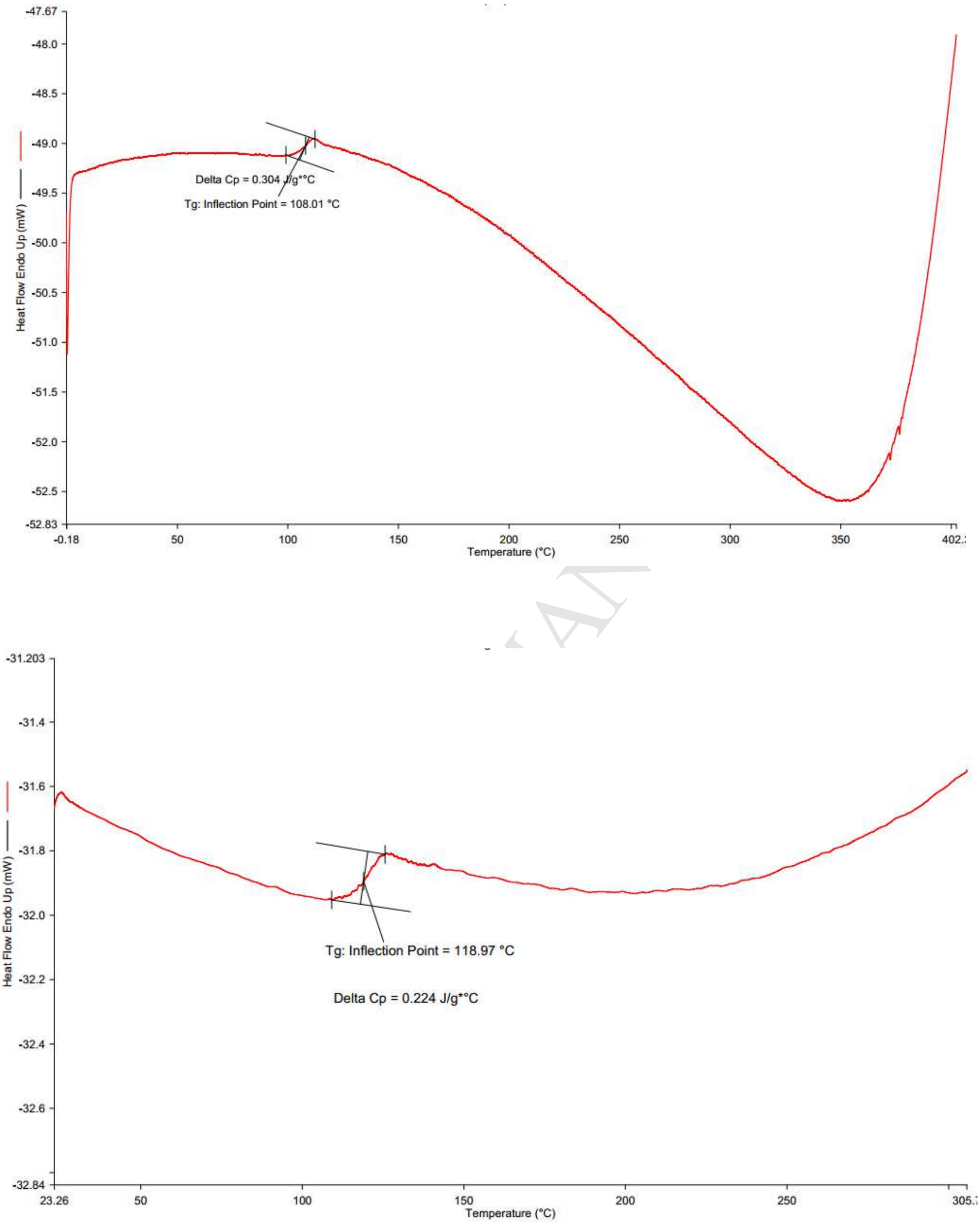


Figure 2. DSC thermograph of the copolymer beads (PS/DVB) with 4 and 8 wt.% DVB (top and bottom, respectively)

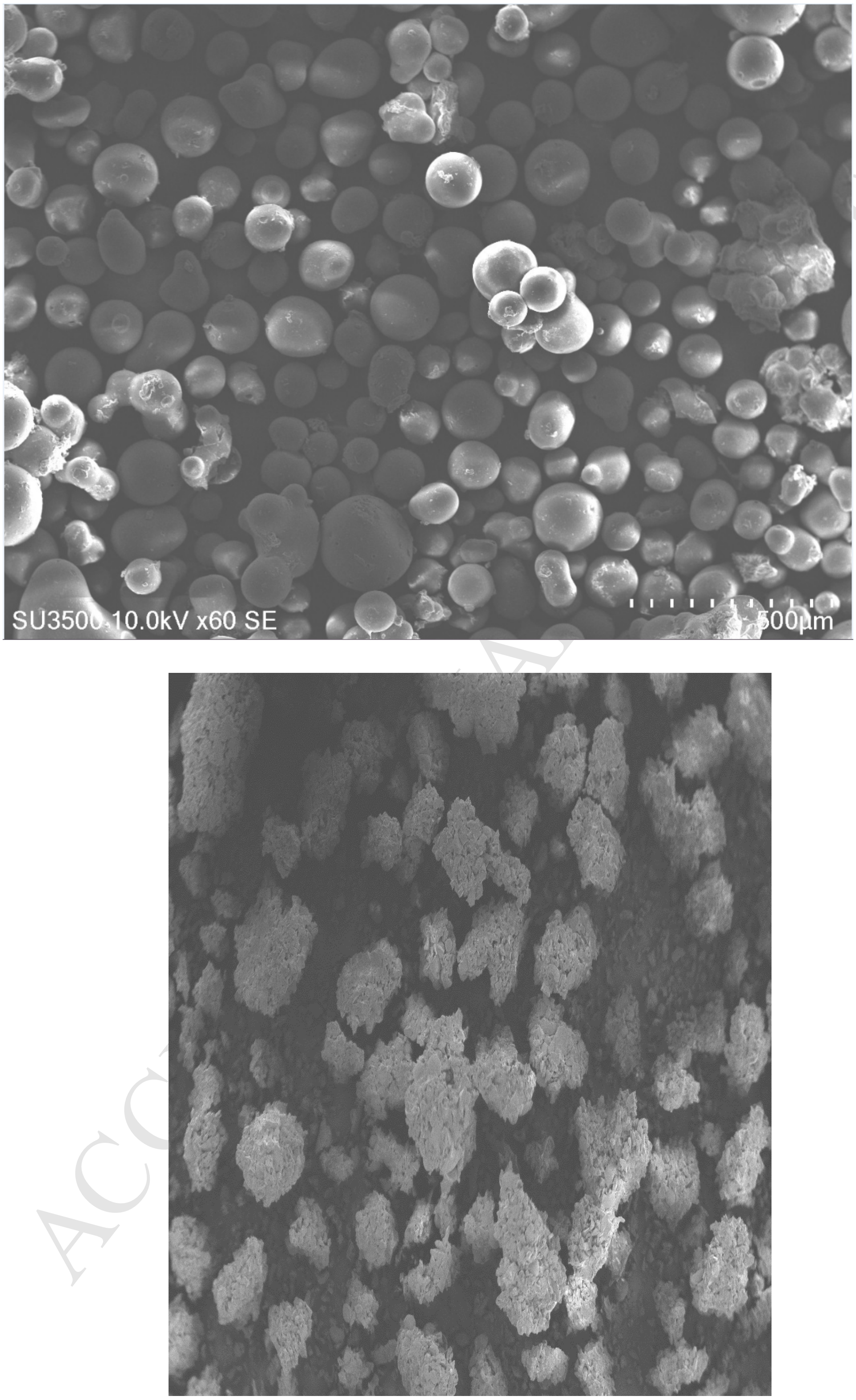


Figure 3. SEM images of PS carrier (up), PS/$TiCl_4$ (down) samples

Highlights

- Polystyrene copolymer beads were prepared by cross-linking suspension copolymerization.
- Polystyrene-$TiCl_4$ coordination complex was prepared through fictionalization of polystyrene.
- A tightly bound complex, polystyrene-$TiCl_4$ was efficient for the modified Mannich reaction.
- The polymeric catalyst was recovered and reused several times