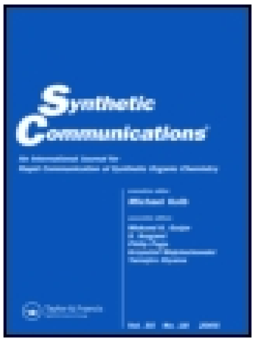


Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Titanium tetrachloride incorporated crosslinked polystyrene copolymer as an efficient and recyclable polymeric Lewis acid catalyst for the synthesis of Β-amino carbonyl compounds at room temperature

Ali Rahmatpour, Reza Eeimen & Niloofar Goodarzi

To cite this article: Ali Rahmatpour, Reza Eeimen & Niloofar Goodarzi (2019): Titanium tetrachloride incorporated crosslinked polystyrene copolymer as an efficient and recyclable polymeric Lewis acid catalyst for the synthesis of Β-amino carbonyl compounds at room temperature, Synthetic Communications, DOI: 10.1080/00397911.2019.1650379

To link to this article: https://doi.org/10.1080/00397911.2019.1650379

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1650379

Titanium tetrachloride incorporated crosslinked polystyrene copolymer as an efficient and recyclable polymeric Lewis acid catalyst for the synthesis of *B*-amino carbonyl compounds at room temperature

Ali Rahmatpour, Reza Eeimen, and Niloofar Goodarzi

Polymer Research Laboratory, Faculty of Chemistry, Shahid Beheshti University, Tehran, Iran

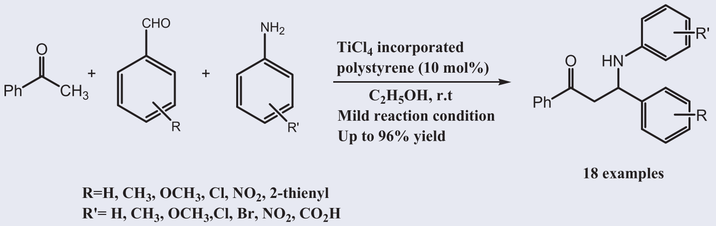
ABSTRACT

An efficient and eco-friendly procedure for one-pot synthesis of β-amino carbonyl compounds by three-component reaction of aromatic aldehydes, acetophenone, and aromatic amines via a Mannich type reaction using a stable tightly bound complex, titanium tetrachloride incorporated crosslinked polystyrene copolymer (PS/$TiCl_4$), as a water tolerant, recoverable, and reusable polymeric Lewis acid catalyst in ethanol at room temperature is reported. The complex of the polystyrene and $TiCl_4$ provides a shelf-stable acidic, water tolerant material, and it is not easily hydrolyzed by water. Our findings thus show a novel and improved modification of the Mannich type reaction in terms of mild reaction conditions, clean reaction profiles, applicability to various substrates using a simple workup procedure which makes this reaction an interesting alternative to previously applied procedures. The recyclability of the catalyst makes this protocol environmentally benign.

ARTICLE HISTORY
Received 10 May 2019

KEYWORDS
β-Carbonyl compounds; cross-linked polystyrene; heterogeneous catalysis; Lewis acid; macromolecular support; Mannich reaction; polystyrene-supported catalyst

GRAPHICAL ABSTRACT



Introduction

Lewis acid-catalyzed reactions are among the less environmentally friendly industrial processes, hence there is a real and urgent necessity to develop heterogeneous solid Lewis acid catalysts for this reaction type. One way to convert corrosive strong Lewis acids into environmentally friendlier catalysts is to heterogenize soluble Lewis acids

---

CONTACT Ali Rahmatpour a_rahmatpour@sbu.ac.ir Polymer Research Laboratory, Faculty of Chemistry, Shahid Beheshti University, PO Box 19839-4716, Tehran, Iran.

Supplemental data for this article can be accessed on the publisher's website.

used in liquid-phase reactions by supporting them on high-surface-area solids such as Al_2O_3, zeolites, clays, etc.[1,2] The type of material used as support frequently plays a crucial role in the performance of the resulting supported catalyst. Polymer supports, also referred to as polymeric reagents and functional polymers, are beaded or microspherical polymer products with a particle size range of about 5–500 µm.[3] Basically, the support has to be thermally and chemically stable during the reaction process and has to provide accessibility and good dispersion of the active sites. Organic polymers as supports provide several potential advantages over the inorganic materials. Many polymers are chemically inert over a large span of pH values (acidic and basic) and resistant to microbiological attack. Polymers allow a large variation of morphology as indicated by the shape, form, cross-linker content, and swellability, allowing the synthesis of highly swellable non-porous as well as highly porous non-swellable materials as films, pellets, powders, or beads. Other great advantages of polymers are their large loading capability of active sites and the wealth of different routes of modification and chemical functionalization. Cross-linked polystyrenes form the basis of many commercial polymer catalysts.[4–6] Due to its large chemical tolerance towards acids and bases, while being widely functionalizable at the aromatic rings, it offers versatile catalyst support, especially for organic synthesis and industrial processes carried out below approximately 200 °C.

$TiCl_4$ is an acid catalyst in a homogeneous medium. A wide variety of reactions in the homogeneous phase employing $TiCl_4$ as an efficient catalyst is reported in the literature.[7–10] Though there are numerous advantages in a homogeneous environment, the major drawbacks of $TiCl_4$ as a catalyst lie in its corrosive nature, moisture sensitivity, less stability at room temperature, risks in handling, a hazardous nature, disposal and regeneration due to its toxic and corrosive nature, containment, and difficulties in separation from reaction mixture. Moreover, reports on the safety of titanium tetrachloride show that its toxicity is high ($LD50 = 464$ mg/kg).[11] Therefore, heterogenization of $TiCl_4$ with suitable catalyst support is an efficient way to find new environmentally friendly catalyst with high catalytic potential. From the standpoint of environmentally benign organic synthesis, the development of highly active and easily reusable immobilized catalysts and the use of benign solvent such as ethanol instead of organic solvent are of great interest to chemists.

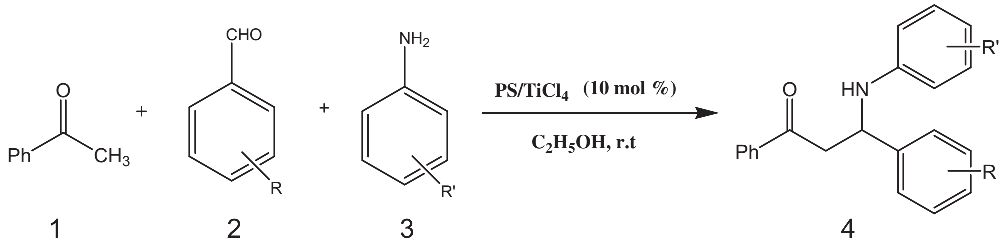
Among nitrogen-containing compounds, β-amino carbonyl scaffolds are gaining importance in organic chemistry because of their abundance in a variety of naturally occurring products and biologically active compounds.[12] β-Amino ketone derivatives are generally prepared by one-pot three-component reaction of a ketone, an aldehyde, and an amine via a Mannich type reaction using various catalysts with *in situ* formation of imines from aldehydes and amines that allows for a wide range of structural variations. Because of the importance of different β-amino ketone derivatives, various catalytic procedures involving aldehydes, ketones, and arylamines using Lewis acid catalysts such as metal triflates and –chlorides,[13–22] Brönsted and heteropoly acid catalysts,[23–25] organocatalysts,[26–31] ionic liquids,[32–36] SiO_2–OSO_3H, SiO_2–$AlCl_3$,[37,38] and recently nanoparticles have been developed for the synthesis of this nitrogen-containing compound.[39,40] However, some of the reported methods suffer from one or more of the disadvantages such as the use of a large amount of catalysts, toxic reagents and solvents, and unsatisfactory reaction times and yields. Most importantly, most catalysts suffer from the drawback of difficult separation after the reactions and therefore are incapable of being recycled and reused. Furthermore, some of them are corrosive and volatile and often cause environmental problems, which limit their use in the synthesis of nitrogen-containing important compounds. Hence, an environmentally benign methodology for the preparation of such compounds is of great concern in synthetic organic chemistry.

Recently, we have successfully synthesized the cross-linked polystyrene copolymer beads with the given particle size and morphology by carrying out aqueous cross-linking suspension copolymerization and incorporated lewis acids into the framework of cross-linked polystyrene copolymer beads, combining the properties such as catalyst selectivity and activity with the ease of separation and catalyst reuse.[41] Immobilizing homogeneous Lewis acids such as $TiCl_4$ on crosslinked PS as a support in one step without functionalization of the copolymer bead matrix via complex formation ($PS/TiCl_4$) is a suitable strategy to create surface-active acidic sites on polystyrene and the resulting polymeric lewis acid can be effective as a heterogeneous catalyst for organic transformations. It has several advantages such as mild acidity, nontoxic nature, safe, easy to handle and store, stability at high temperature and provides experimental simplicity.

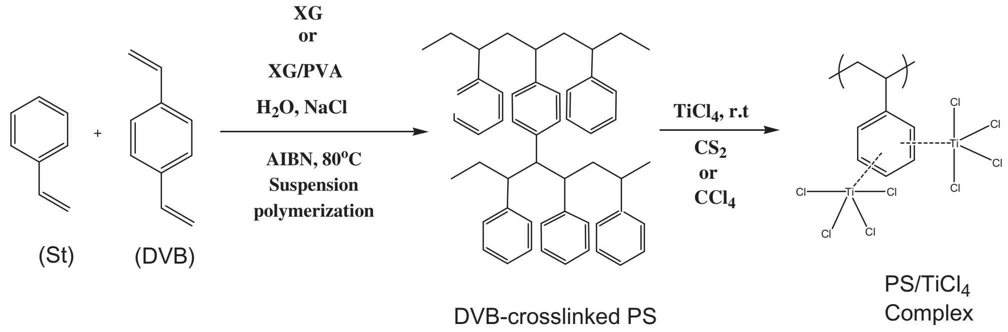
In the continuation of our research in using recoverable polymeric acids as catalysts in organic transformation,[42–44] in this letter, we present the results of an extended investigation on the activity of the titanium tetrachloride-functionalized crosslinked polystyrene, a stable tightly bound complex $PS/TiCl_4$, as a recyclable catalyst in Mannich reactions leading to the formation of β-amino ketone derivatives. We have developed a convenient synthetic method for one-pot synthesis of β-amino carbonyl compounds **4a**-**r** via the condensation of acetophenone **1**, aromatic aldehydes **2** and aromatic amines **3** in the presence of $TiCl_4$-incorporated crosslinked polystyrene as a heterogeneous polymeric Lewis acid catalyst at room temperature in high yields (Scheme 1). The reaction takes place in ethanol as a green reaction medium at ambient temperature. To the best of our knowledge, this is the first report for the synthesis of β-amino carbonyl compounds over titanium tetrachloride-incorporated crosslinked polystyrene copolymer.

Results and discussion

The polymeric carrier beads (PS/DVB) as supports were readily synthesized by an aqueous suspension radical copolymerization technique using styrene and divinylbenzene



Scheme 1. Mannich reaction of acetophenone and various aromatic aldehydes and aromatic amines catalyzed by $PS/TiCl_4$.



Scheme 2. Schematic representation of the procedure for the synthesis of polymeric carrier and its titanium tetrachloride complex.

monomers as we described previously.[41] The incorporation of homogeneous titanium tetrachloride Lewis acid into the framework of cross-linked polystyrene copolymer beads was achieved by the addition of two components in dry CCl_4 or CS_2 solvent under reflux conditions in a one-step reaction leading to the polystyrene-supported $TiCl_4$ catalyst (0.824 mmol g^{-1}- $TiCl_4$ loading). The procedure for the synthesis of (PS/$TiCl_4$) is depicted in Scheme 2. The complex formation takes place via the formation of a coordination bond between the $TiCl_4$ and the PS carrier. The incorporation of $TiCl_4$ Lewis acid onto polystyrene was verified by FT-IR, UV, pH measurement, TGA, XRD, SEM, BET and ICP techniques (see supplemenrtary data).

To validate our hypothesis and achieve catalytic evaluation of PS/$TiCl_4$ complex, we took the synthesis **4a** from aniline, benzaldehyde, and acetophenone as the model reaction. The results are summarized in Table 1. A blank reaction was carried out using equivalent amounts of aniline, benzaldehyde, and acetophenone. The reaction was conducted at room temperature in ethanol; even after 8 h, no product was obtained. The same reaction was performed using PS/$TiCl_4$ as the catalyst and ethanol as a reaction medium at room temperature. Surprisingly, 93% yield of desired product was obtained after stirring the reaction mixture for 2.1 h (Scheme 2). Initial experiments, 10 mol% of catalyst was tested using 1.0 mmol of each substrate in ethanol at room temperature for 2.1 h. We further investigated the optimum reaction conditions using different amounts of PS/$TiCl_4$ and it was found that the yields were obviously affected with different amount of catalyst. An increase in the quantity of PS/$TiCl_4$ from 2 to 5 mol% not only decreased the reaction time from 8 to 5 h, but also increased the product yield slightly from 43 to 69% (Table 1, entries 8,9). This showed that the catalyst concentration plays a major role in the optimization of the product yield. No reaction was observed in the absence of catalyst, while 10 mol% of PS/$TiCl_4$ was sufficient to drive the reaction completely and an excessive amount of catalyst did not increase the yields significantly (Table 1, entries 7,10). Subsequently, various solvents were screened in the same reaction condition. Results demonstrated that the high yield of desired product **4a** was achieved with ethanol solvent. The reaction in toluene afforded very poor yields whilst the use of THF, $CHCl_3$, CH_3CN, and DMF afforded moderate yields (Table 1, entries 1-5). Ethanol was chosen as the solvent system for this conversion, because of its swellability with the catalyst and miscibility with the substrates. No reaction occurred when H_2O was used as a solvent, maybe because of the aggregation of the catalyst, caused by

Table 1. Optimization of the reaction conditions of the PS/$TiCl_4$-catalyzed one-pot reaction of acetophenone, benzaldehyde, and aniline[a].

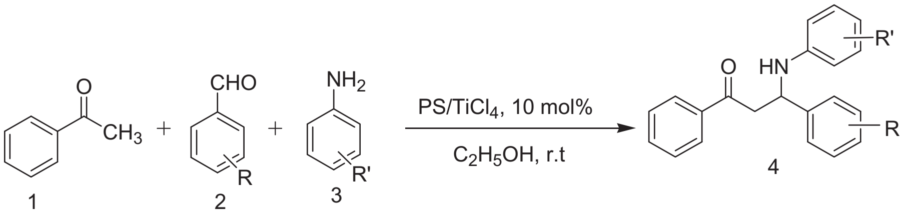
Entry	Solvent	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	Toluene	10	8	34
2	THF	10	8	48
3	$CHCl_3$	10	8	45
4	DMF	10	8	56
5	CH_3CN	10	8	55
6	H_2O	10	8	NR[d]
7c	C_2H_5OH	–	8	NR
8	C_2H_5OH	2	8	43
9	C_2H_5OH	5	5	65
10	C_2H_5OH	10	2.1	93
11[e]	C_2H_5OH	10	1.5	81
12[f]	C_2H_5OH	10	1.1	70
13[g]	C_2H_5OH	–	6	NR
14[h]	C_2H_5OH	–	2.5	46
15[i]	C_2H_5OH	10	0.5	NR
16[j]	C_2H_5OH	10	3.5	75

[a]Reaction conditions: benzaldehyde (1 mmol), aniline(1 mmol), acetophenone (1 mmol), ethanol (3 mL), room temperature (refers here to 30 °C).
[b]Isolated yield.
[c]No catalyst.
[d]NR: No reaction.
[e,f]The reactions were conducted at 60 and 80 °C, respectively.
[g]PS was used as catalyst.
[h]The ethylbenzene-$TiCl_4$ complex was used as catalyst.
[i]Catalyst was filtered after 50 min.
[j]PS/$AlCl_3$ (capacity: 0.47 mmol/g) was used as a catalyst.

its hydrophobic nature, led to inadequate access of the substrates to the active sites of the catalyst (Table 1, entry 6). Finally, the data in Table 1 demonstrates the susceptibility of the reaction to the solvent in which the reactions carried out. Thus, for the model reaction, much higher product yields are obtained with solvents capable of swelling the polymer. Among the various solvents tested, ethanol serves to swell the polymer and make the titanium chloride more accessible.

To optimize the reaction temperature, we carried out a study using the model substrates in ethanol at different temperatures (Table 1, entries 11,12). Increasing the temperature to 80 °C favored side reactions and the formation of deeply colored products. If the reaction runs at refluxing temperature, no Mannich reaction base can be isolated. Decreasing the temperature decreases the rates of the reaction and also the rates of the side reactions. It was found that the room temperature was an appropriate condition in terms of reaction time and yield obtained for PS/$TiCl_4$-catalyzed one-pot three-component Mannich reaction. After several trials, the best result with 93% yield was obtained by carrying out the reaction with 1:1:1:0.1 molar ratio of acetophenone, benzaldehyde, aniline, and PS/$TiCl_4$ complex at room temperature in 3 ml of ethanol for 2.1 h.

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 cross-linked PS, we have performed the catalytic reaction of acetophenone, benzaldehyde and aniline in the presence of ethylbenzene-$TiCl_4$ as the homogeneous phase at room temperature in C_2H_5OH (Table 1, entry 14). 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



Scheme 3. Synthesis of β-carbonyl compounds from acetophenone and various aromatic aldehydes and aromatic amines catalyzed by PS/$TiCl_4$.

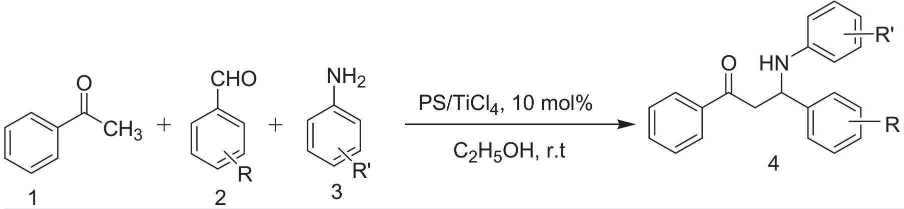
much higher than the homogeneous complex catalyst. To confirm the catalytic activity of PS/$TiCl_4$, a comparison experiment was carried out by using pristine PS alone under the same experimental conditions; no reaction occurred and the starting components remained unreacted (Table 1, entry 13). This indicated that the PS itself did not promote the reaction. 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).

To discover 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 50 min and then isolated by filtration. When the reactants were added to the filtrate and stirred for 2.5 h, no reaction took place (Table 1, entry 15). These results indicated that the reaction takes place in the solid matrix and the release of $TiCl_4$ is negligible.

Due to the success of the above reaction, the substrates scope of this protocol was then investigated using the optimized conditions. As shown in Scheme 3, a variety of both aldehydes **2** and substituted anilines **3** were reacted with acetophenone **1** in the presence of PS/$TiCl_4$, to afford the desired β-amino carbonyl compounds **4a-r** in good to excellent yields (82–96%). The results are summarized in Table 2. Corresponding product yields depended on steric hindrance and electronic effect of substrates. Reaction of aromatic aldehyde substrates with an electron-withdrawing group (–Cl, –NO_2, including –H) produced good yields (Table 2, 12–16,18,1–9). While aromatic aldehyde substrates with an electron-donating group (–OCH_3,–CH_3) provided products in very good yields (Table 2, entries 10,11,17). Aromatic amine substrates (*m*-and *p*-substituted) gave good results, while *o*-substituted amines (Table 2, entry 3) failed to yield any desired product due to steric hindrance of *ortho*-substituents. Furthermore, amines bearing electron-withdrawing groups gave the desired product in good yields (Table 2, entries 4, 6–9). The use of aliphatic aldehydes (such as butyl aldehyde, propionaldehyde, and *n*-octanal) and aliphatic amines (such as propylamine, ethylamine, and benzyl amine) failed to furnish the desired products, which implies that this reaction is limited to nonenolizable imines. In addition, the heteroaromatic aldehydes, such as 2-thiophene carboxaldehyde, was used as a starting material in our reaction conditions and well-tolerated with this protocol and the results are now provided in Table 2 (entry 19).

A proposed mechanism for the synthesis of β-amino carbonyl compounds **4** is presented in Scheme 4. Initially, the complex formation increases the activity of the carbonyl carbon atom of aromatic aldehydes by which it undergoes nucleophilic attack by amine and generates the imine intermediate **II** after dehydration. Next, the imine intermediate activated by Ti(IV) as Lewis acid undergoes a nucleophilic attack by enol which

Table 2. PS/TiCl$_4$ catalyzed synthesis of various β-amino carbonyl compounds **4**[a,b].



Entry	R	R′	Product	Time/h	Yield[c]/%	M.p(°C) Found
1	H	H	**4a**	2.1	93	168–169
2	H	4–CH_3	**4b**	2.5	96	168–170
3	H	2–CH_3	**4c**	8	Trace	–
4	H	4–Cl	**4d**	2	90	167–168
5	H	4–OCH_3	**4e**	2.1	161–162	
6	H	4–Br	**4f**	2	94	182–184
7	H	4–NO_2	**4g**	2.5	82	184–185
8	H	3–NO_2	**4h**	2.1	91	138–139
9	H 4–CO_2	H	**4i**	2.5	89	192–194
10	4–CH_3	H	**4j**	3.1	95	130–132
11	4–OCH_3	H	**4k**	3.1	94	149–150
12	4–Cl	H	**4l**	2.1	93	128–129
13	4–NO_2	H	**4m**	2.1	89	108–110
14	F	H	**4n**	2.3	88	102–104
15	4–Cl	4–Cl	**4o**	2.5	87	119–121
16	4–NO_2	4–Cl	**4p**	3.5	90	128–129
17	4–OCH_3	4–Cl	**4q**	2.2	91	159–160
18	4–Cl	3–NO_2	**4r**	3	85	131–133
19	2–Thienyl	H	**4s**	2.5	90	172–173

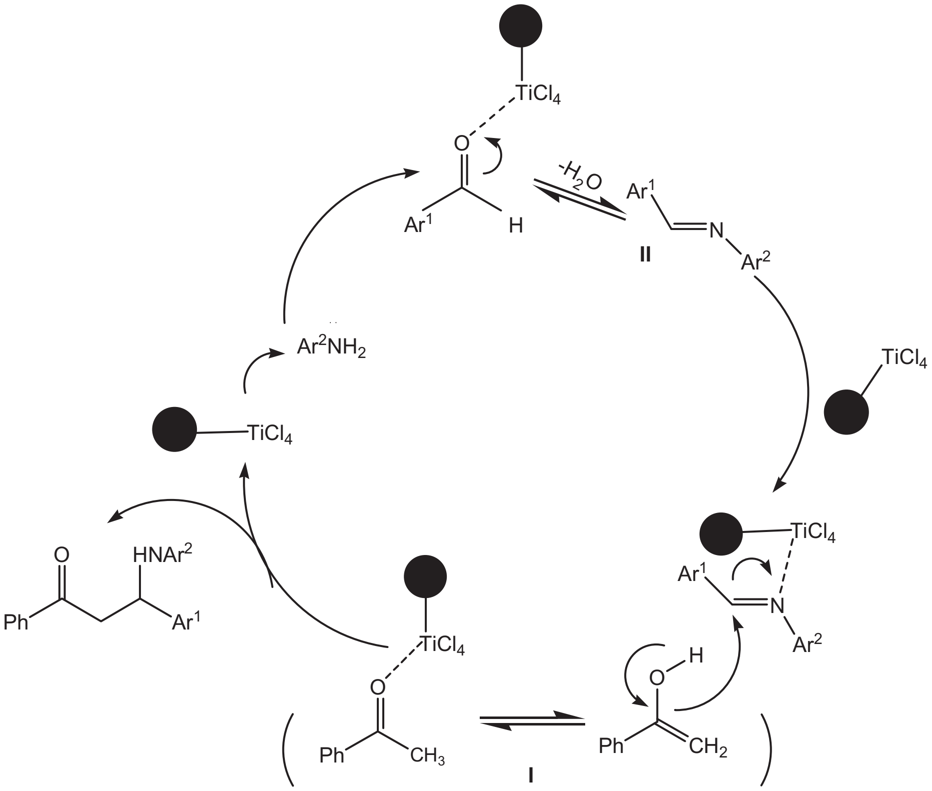
[a] Reaction conditions: All reactions were conducted with aniline (**3a**, 1 mmol), benzaldehyde (**2a**, 1 mmol), acetophenone (**1**, 1 mmole) using PS/TiCl$_4$ (10 mol%) in ethanol (3 mL) at room temperature.

[b] All products were characterized by comparison of their melting points, IR, and ^{1}H NMR spectra with those of authentic samples.[20,21,38,39,47–50]

[c] Yields refer to the isolated products.

in turn converts to the final product and simultaneously releases the catalyst for the next catalytic cycle. We monitored aldehyde consumption by GC analysis and it turned out that the Schiff base is formed (within the first 20 min of the beginning of the reaction), indicating that the rate-determining step was to be the attack of *in-situ* generated enolate **I** on the *in-situ* generated aldimine **II** as shown in Scheme 4. The proposed mechanism is consistent with the literature.[48]

In order to verify the recyclability of the catalyst and if the catalyst could be reused, three-component reaction under similar conditions, between benzaldehyde, aniline, and acetophenone, was taken as the representative case. After the reaction was over, the catalyst was separated from the reaction mixture by filtration, washed with ethanol followed by diethyl ether. Then, the recovered catalyst was dried at 50 °C under vacuum for 6 h and used for a further five additional reaction cycles. In all cases, the PS/TiCl$_4$ catalyst exhibited consistent catalytic activity, establishing the recycling and reusability of the catalyst without any significant loss in the yield of the product. Only a very small drop in the product yield in each catalytic cycle is observed (Table 3). Along these lines, there were no significant differences between the IR spectra of the fresh and recovered catalyst, which may indicate there was no degradation of the supported catalyst. The extent of TiCl$_4$ leaching from the catalyst was very low ($<$10 ppm) as judged by ICP analysis. From the first run to the fifth run, the titanium content of the recovered catalyst remained almost the same. All these results confirmed that our catalyst is stable and has practical utility.



Scheme 4. Proposed mechanism for the formation of **4.**

Table 3. Recycling potential of the PS/$TiCl_4$ for the Mannich reaction[a].

No of cycles	Fresh	Run 1	Run 2	Run 3	Run 4	Run 5
Yield[b](%)	93	92	91	90	90	89
Time (h)	2.1	2.1	2.2	2.4	2.5	3

[a]Reaction conditions: benzaldehyde (1 mmol), aniline (1 mmol), acetophenone (1 mmol), room temperature, catalyst (10 mol%).

[b]Isolated yield of pure product.

In Table 4, the condition and efficiency of $TiCl_4$-functionalized polystyrene copolymer catalyst were compared with some other catalysts in the synthesis of **4a**. The results showed that in this work, disadvantages of some of the previous reports such as long reaction times and low yields have been decreased. In addition, the efficiency of the present reaction was increased.

Conclusion

In total, we presented a new catalytic protocol for the efficient synthesis of β-amino ketone derivatives via one-pot three-component Mannich reaction of various aromatic aldehydes, acetophenone, and aromatic amines in the presence of a tightly bound complex of styrene-divinylbenzene copolymer/$TiCl_4$ as a reusable polymeric Lewis acid

Table 4. Comparison of the polymeric catalyst PS/$TiCl_4$ with various homogeneous or heterogeneous catalysts in Mannich reactions for the synthesis of **4a**.

Entry	Catalyst	Solvent	T (°C)	Time (h)	Yield (%)	[Ref.]
1	$BiCl_3$	EtOH	r.t.	11	95	[49]
2	H_3Pmo_{12} O_{40}	H_2O	r.t.	18	76	[27]
3	DBSA	H_2O	23	12	69	[24]
4	$FeCl_3$	EtOH	r.t.	24	n.r.	[22]
5	$NbCl_5$	EtOH	r.t.	12	95	[20]
6	Yb(OPf)3 Rare earth (III) perfluorooctane sulfonates	$PhCH_3/C_6F_5CF_3$		12	98	[52]
7	Pyridiniumtrifluoroacetate	Solvent-free	r.t.	8	82	[53]
8	[$NaBArF_4$]	H_2O	r.t.	48	81	[51]
9	$FeCl_3$	EtOH	r.t.	20	0	[38]
10	$ZnCl_2$	EtOH	r.t.	20	0	[38]
11	$SnCl_2$	EtOH	r.t.	10	93	[54]
12	$SiO_2/AlCl_3$	EtOH	r.t.	5	93	[38]
13	$SiO_2/SbCl_3$	EtOH	r.t.	4	93	[55]
14	PS-SO_3H	H_2O	r.t.	24	75	[56]
15	PSt/$AlCl_3$ (10 mol%)	EtOH	r.t.	3.5	75	This work
16	PSt/$TiCl_4$ (10 mol%)	EtOH	r.t.	2.1	93	This work

n.r.: no reaction; r.t. refers to 30 °C.

catalyst in ethanol medium. This method has the advantages of high yields, mild reaction conditions, short reaction time, avoiding hazardous organic solvents, convenient procedure, and environmental friendliness. The catalyst shows not only high catalytic activity, but also offers many practical advantages such as thermal stability and recyclability. Notably, the PS/$TiCl_4$ catalyst could be recovered and reused several times without a significant loss in its activity. The waste-free process combined with recovery and reusability of the catalyst makes this method economic and benign for the synthesis of β-amino carbonyl compounds.

Experimental

Materials and instrumentations

All of the information about the materials and instrumentations used in this work were presented in the Supporting information.

Preparation of crosslinked-polystyrene carrier

The preparation of the support was designed by the sequence of reactions given in Scheme 2. The cross-linked polystyrene copolymer beads were prepared and characterized as we described previously.[41]

Preparation of $TiCl_4$-functionalized polystyrene copolymer

The as-prepared polystyrene beads (8% DVB) was dispersed in 6 mL of dry CCl_4 (or CS_2) solvent and left to swell under intense stirring for 30 min at room temperature. A solution of anhydrous $TiCl_4$ (2 g) in dry carbon disulfide (4 mL) was added to the above dispersion under magnetic stirring followed by refluxing in an oil bath for 1 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and cold water (50 mL) was then cautiously added to hydrolyze the uncomplexed $TiCl_{4.}$ Finally, the solid was collected using the suction filtration followed by washing with diethyl ether and chloroform and was dried in a vacuum oven overnight at 50 °C. The loading of $TiCl_4$ measured by the Mohr titration method (0.824 mmol/g)

General procedure for the one-pot three-component Mannich-type reaction

A mixture of aromatic aldehydes (1 mmol), acetophenone (1 mmol), aromatic amines (1 mmol), and PS/$TiCl_4$ containing certain amount of $TiCl_4$ (0.15 gr, 0.1 mmol of $TiCl_4$) in anhydrous ethanol (3 mL) was stirred at room temperature for a period of time listed in Table 2 indicated by TLC or GC. After completion of the reaction, the 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 with ethanol and dried at 60 °C for 6 h and stored in a desiccator. The crude product was purified by recrystallization from ethanol or ethanol-acetone (3:2, *v/v*) to afford the pure product. A 10 mmol-scale reactions were also carried out without any difficulties. All of the products were characterized by comparison of their physical data, FTIR, and ^1H NMR spectra with those of authentic samples.

The characteristic data of selected compounds

3-Anilino-1,3-diphenyl-1-propanone (Table 2, entry 1, 4a, $C_{21}H_{19}NO$)[39]

Colorless solid, mp = 168–169 °C, IR (KBr, cm^{-1}) ν: 3385 (NH), 2383, 1665 (CO), 1549, 1509, 1450, 1367, 1287, 1216, 1070, 992, 857, 743, 688 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.90$ (2H, d, $J = 8.50$ Hz), 7.54 (2H, t, $J = 7.30$ Hz), 7.22–7.46 (6 H, m), 7.10 (2H, t, $J = 7.50$ Hz), 6.76 (1H, t, $J = 7.30$ Hz), 6.69 (2H, d, $J = 7.8$ Hz), 5.0 (1 h, t, $J = 6.50$ Hz), 3.59 (2H, d, $J = 5.80$ Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 46.20$, 55, 95.2, 114.0, 117.6, 118.10, 126.3, 125.1, 127.4, 128.2, 128.7, 128.8, 129.1, 129.3, 133.4, 136.6, 142.7, 146.6, 159.1, 179.2, 198.2. Anal. Calcd. for $C_{21}H_{19}NO$: C 83.69, H 6.35, N 4.65%; Found: C 83.74, H 6.41, N 4.56%.

3-(4-chloro-phenylamino)-1,3-diphenylpropanone (Table 2, entry 4, 4d, $C_{21}H_{18}NO$)[38,39]

Colorless solid, mp = 167–168 °C, IR (KBr, cm^{-1}) ν: 3369 (NH), 3010, 2320, 1661 (CO), 1594, 1490, 1448, 1405, 1280, 851, 745, 681 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 3.41$–3.50 (m, 2H), 4.65 (br, 1H), 4.92–4.94 (m,1H), 6.45–6.47 (m, 2H, ArH), 7.00–7.02 (m, 2H, ArH), 7.21–7.24 (m, 1H, ArH), 7.30–7.33 (m, 2H, ArH), 7.39–7.46 (m, 4H, ArH), 7.54–7.58 (m, 1H, ArH), 7.88–7.90 (m, 2H, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 46.3$, 55.0, 115.0, 122.5, 126.4, 127.6, 128.3, 128.8, 129.0, 129.1, 133.6, 136.6, 142.6, 145.6, 198.3. Anal. Calcd. for $C_{21}H_{18}NO$: C 75.11, H 5.40, N 4.17%; Found: C 75.15, H 5.30, N 4.23%.

3-(4-Methoxy-phenylamino)-1,3-diphenyl-propanone (Table 2, entry 5, 4e, $C_{21}H_{22}NO_2$)[21]

Colorless solid, mp = 161–162 °C, IR (KBr, cm^{-1}) ν: 3385 (NH), 1675 (CO) cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.81 (d, J = 7.5 Hz, 2H, Ar–H), 7.53–7.33 (m, 1H, Ar–H), 7.41–7.38 (m, 2H, Ar–H), 7.30–7.24 (m, 2H, Ar–H), 7.15 (d, J = 8.3 Hz, 2H, Ar–H), 6.96–7.05 (m, 1H, Ar–H), 6.71 (d, J = 8.9, 2H, Ar–H), 6.51 (d, J = 8.6 Hz, 2H, Ar–H), 4.86 (t, 1H), 3.58 (s, 3H, -OCH$_3$), 3.44–3.39 (m, 2H). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 46.2, 55.3, 58.2, 115.2, 122.7, 126.2, 127.1, 128.6, 128.8, 128.9, 129.3, 132.5, 138.5, 141.7, 1510.2, 195.6. Anal. Calcd. for $C_{21}H_{22}NO_2$: C 79.73, H 6.39, N 4.23%; Found: C 79.59, H 6.70, N 4.38%.

3-(4-Bromoanilino)-1,3-diphenyl-1-propanone (Table 2, entry 6, 4f, $C_{21}H_{18}BrNO$)[21]

Colorless solid, mp = 182–184 °C, IR (KBr, cm^{-1}) ν: 3380, 1676 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.86 (2H, d, J = 8.2 Hz), 7.51 (2H, t, J = 7.3 Hz), 7.39 (2H, t, J = 7.5 Hz), 7.5 (2H, d, J = 7.5 Hz), 7.20–7.28 (4H, m), 6.77 (2H, d, J = 8.8 Hz), 4.99 (1H, t, J = 6.5 Hz), 3.85 (2H, d, J = 6.5 Hz). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 43.7, 59.1, 114, 114.9, 120.7, 121.2, 124.1, 127.9, 128.1, 128.6, 128.7, 128.9, 132.2, 133.6, 136.2, 137.6, 138, 139.3, 144.9, 162.9, 196.6. Anal. Calcd. for $C_{21}H_{18}BrNO$: C 66.32, H 4.77, N 3.66%; Found: C 66.28, H 4.70, N 3.70%.

3-(4-Nitro-phenylamino)-1,3-diphenyl-propanone (Table 2, entry 7, 4 g, $C_{21}H_{18}N_2O_3$)[21]

Colorless solid, mp = 184–185 °C, IR (KBr, cm^{-1}) ν: 3365 (NH), 1628 (CO) cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.67 (d, J = 6.80 Hz, 2H), 5.12 (t, 1H), 6.37 (brs, 2H, Ar–H), 6.64 (d, J = 6.4, 2H, Ar–H), 7.24–7.20 (m, 1H, Ar–H), 7.38–7.29 (m, 2H, Ar–H), 7.37 (d, J = 7.70 Hz, 2H, Ar–H), 7.67–7.59 (m, 1H, Ar–H), 8.01 (d, J = 7.2 Hz, 2H, Ar–H). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 45.2, 53.1, 111.7, 125.9, 126.1, 127.4, 128.9, 128.2, 128.1, 130.5, 132.8, 136.7, 138.6, 140.0, 197.8. Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.82, H 5.24, N 8.09%; Found: C 72.42, H 5.76, N 7.96%.

4-((3-oxo-1,3-diphenyl) propylamino)-benzoic acid (Table 2, entry 9, 4i, $C_{22}H_{19}NO_3$)[21]

Colorless powder, mp = 192–194 °C, IR (KBr, cm^{-1}) ν: 3368 (NH), 2947, 1669 (CO), 1608, 1273, 708 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 11.90 (1H, s, COOH), 7.95 (2H, d, J = 7.46 Hz, ArH), 7.62 (1H, t, J = 7.36 Hz, ArH), 7.58 (2H, d, J = 8.79 Hz, ArH), 7.50 (2H, t, J = 7.72 Hz, ArH), 7.42 (2H, d, J = 7.43 Hz, ArH), 7.30 (2H, t, J = 7.61 Hz, ArH), 7.19 (1H, t, J = 7.33 Hz, ArH), 6.90 (1H, d, J = 7.36 Hz, ArH), 6.50 (2H, t, J = 8.73 Hz, ArH), 5.55 (1H, m, NCH), 3.62 (1H, m, COCH$_2$), 3.58 (1H, m, COCH$_2$). Anal. Calcd. for $C_{22}H_{19}NO_3$: C 76.52, H 5.50, N 4.058%; Found: C 76.42, H 5.43, N 4.095%.

3-Anilino-3-(4-methylphenyl)-1-phenyl-1-propanone (Table 2, entry 2, 4j, $C_{22}H_{21}NO$)[21]

Colorless powder, mp = 130–132 °C, IR (KBr, cm^{-1}) ν: 3387, 1667 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 7.92$, 2H, d, $J = 7.30$ Hz), 7.55 (1H, t, $J = 8.80$ Hz, 7.44 (2H, t, $J = 7.80$ Hz), 7.32, 2H, d, $J = 8.0$ Hz), 7.05–7.15 (4H, m), 6.64 (1H, t, $J = 7.30$ Hz), 6.58 (2H, d, $J = 8.80$ Hz), 4.98 (1H, t, J = 6.0 Hz), 3.50 (2H, d, $J = 5.50$ Hz), 2.22 (3 H, s). ^{13}C NMR (62.9 MHz, CDCl$_3$): $\delta = 21.1$, 46.2, 54.7, 114.0, 114.9, 118.0, 124.4, 126.3, 127.3, 127.9, 128.2, 128.6, 129.1, 129.4, 133.2, 136.3, 139.0, 141.7, 145.5, 147.9, 159.0, 199.10. Anal. Calcd. for $C_{22}H_{21}NO$: C 83.78, H 6.71, N 4.44%; Found: C 83.80, H 6.73, N 4.39%.

3-Anilino-3-(4-methoxyphenyl)-1-phenyl-1-propanone(Table 2, entry 11, 4k, $C_{22}H_{21}NO_2$)[21]

Colorless solid, mp = 149–150 °C, IR (KBr, cm^{-1}) ν: 3401(NH), 1679(CO) cm^{-1}, ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 7.92$ (2H, d, $J = 8.3$ Hz), 7.88, 1H, t, $J = 8.5$ Hz), 7.45 (2H, t, $J = 7.8$ Hz), 7.34 (2H, d, $J = 8.8$ Hz), 7.10 (2H, t, $J = 7.5$ Hz), 6.8 (2H, d, $J = 8.8$ Hz), 6.68 (1H, t, $J = 8.0$ Hz), 6.60 (2H, d, $J = 7.5$ Hz), 4.97 (1H, t, $J = 6.5$ Hz), 3.80 (3H, s), 3.47 (2H, d, $J = 5.8$ Hz). ^{13}C NMR (62.9 MHz, CDCl$_3$): $\delta = 46.2$, 54.5, 55.2, 114.1, 114.2, 118.0, 123.2, 124.3, 124.9, 127.1, 127.5, 128.2, 128.7, 129.1, 133.3, 134.5, 136.1, 141.2, 145.7, 148.0, 158.8, 194.4. Anal. Calcd. for $C_{22}H_{21}NO_2$: C 79.72, H 6.37, N 4.24%; Found: C 79.69, H 6.44, N 4.19%.

3-Anilino-3-(4-chlorophenyl)-1-phenyl-1-propanone (Table 2[41], $C_{21}H_{18}ClNO$) [47]

Colorless solid, mp =128–130 °C, IR (KBr, cm^{-1}) ν: 3380, 3020, 2370, 1675, 1596, 1511, 1404, 1289, 1089, 991, 825, 746, 687 cm^{-1}. ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 7.89$ (2H, d, $J = 7.0$ Hz), 7.56–7.64 (2 h, m), 7.49 (2H, d, $J = 8.80$ Hz), 7.42 (2H, d, $J = 9.0$ Hz), 7.30 (1H, d, $J = 8.50$ Hz), 7.11 (2 H, t, $J = 8.25$ Hz), 6.70 (1H, t, $J = 8.0$ Hz), 6.54 (2 H, d, $J = 7.80$ Hz), 4.99 (1H, t, $J = 6.50$ Hz), 4.58 (1H, s), 3.46 (2H, d, $J = 5.80$ Hz). ^{13}C NMR (62.9 MHz, CDCl$_3$): $\delta = 46.1$, 54.2, 113.8, 118.1, 122.5, 127.9, 128.2, 128.5, 128.6, 128.8, 128.9, 129.2, 129.6, 132.9, 133.4, 133.5, 136.6, 141.5, 143.2, 146.6, 197.8. Anal. Calcd. for $C_{21}H_{18}ClNO$: C 75.11, H 5.40, N 4.17%; Found: C 75.14, H 5.33, N 4.24%.

3-Anilinio-3-(4-nitrophenyl)-1-phenyl-1-propanone (Table 2, entry 13, 4 m, $C_{21}H_{18}N_2O_3$)

White solid, mp = 108–110 °C, IR (KBr, cm^{-1}) ν: 3372 (NH), 1681 (CO) cm^{-1}, ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 8.10$ (2H, d, $J = 8.80$ Hz), 7.89 (1H, d, $J = 8.0$ Hz), 7.60 (2H, d, $J = 8.5$ Hz), 7.57 (2H, t, $J = 7.3$ Hz), 7.44 (2H, t, $J = 7.8$ Hz), 7.11, 2H, t, $J = 7.5$ Hz), 6.70 (1H, d, $J = 7.30$ Hz), 6.55 (2H, d, $J = 7.8$ Hz), 5.10 (1H, t, $J = 6.0$ Hz), 3.50 (2H, d, $J = 6.0$ Hz). ^{13}C NMR (62.9 MHz, CDCl$_3$): $\delta = 45.5$, 54.4, 114.1, 118.8, 123.6, 124.1, 124.2, 125.7, 127.5, 128.6, 128.8, 129.3, 129.6, 133.4, 133.8, 136.3, 141.5, 145.9, 147.2, 150.5, 197.1. Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C 72.78, H 5.26, N 8.09%; Found: C 72.76, H 5.28, N 8.15%.

3-(4-Fluorophenyl)-1-phenyl-3-(phenylamino)propanone (Table 2, entry 14, 4n, $C_{21}H_{18}FNO$)[38]

Colorless solid, mp = 102–104 °C, IR (KBr, cm^{-1}) ν: 3380 (NH), 3020, 2312, 1672 (CO), 1600, 1548, 1507, 1425, 1167, 1102, 1062, 826, 746, 684 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 3.40–3.49$ (m, 2H), 4.55 (br, 1H), 4.97 (t, 1H, $J = 7.3$ Hz), 6.52–6.54 (m, 2H, ArH), 6.67 (t, 1H, $J = 7.4$ Hz, ArH), 6.97–7.01 (m, 2H, ArH), 7.07–7.11 (m,2H, ArH), 7.38–7.46 (m, 4H, ArH), 7.54–7.56 (m,1H, ArH), 7.88–7.90 (m, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 46.3$, 54.2, 113.9, 115.6, 115.9, 118.1, 128.0, 128.1, 128.3, 128.8, 129.2, 133.7,146.8, 163.3, 198.2. Anal. Calcd. for $C_{21}H_{18}FNO$: C 78.999, H 5.642, N 4.388%; Found: C 78.78, H 5.65, N 4.95%.

Acknowledgments

The authors are thankful to TPC for providing the required chemicals.

Disclosure statement

There are no conflicts of interest to declare.

Funding

The authors are thankful to the Shahid Beheshti University Research Council for partial support of this work [Grant No. 1396].

ORCID

Ali Rahmatpour http://orcid.org/0000-0001-6524-7176

References

[1] Corma, A.; GarcíA, H. Highly Efficient One-Pot Three-Component Mannich Reaction in Water Catalyzed by Heteropoly Acids. *Chem. Rev.* **2003**, *103*, 4307–4365.
[2] Clark, J. H.; Macquarrie, D. J.; Price, P. M. Modified Silicas for Clean Technology. *J. Chem. Soc, Dalton Trans.* **2000**, *2*, 101–110.
[3] Hodge, P. Synthesis of Organic Compounds Using Polymer-Supported Reagents, Catalysts, and/or Scavengers in Bench Top Flow Systems. *Ind. Eng. Chem. Res.* **2005**, *44*, 8542–8553. doi:10.1021/ie040285e.
[4] Hodge, P. Organic Synthesis Using Polymer-Supported Reagents, Catalyst and Scavengers in Simple Laboratory Flow Systems. *Current Opinion in Chem. Biology* **2003**, *7*, 362–373. doi:10.1016/S1367-5931(03)00052-8.
[5] Barbaro, P.; Liguori, F. *Heterogenized Homogeneous Catalysts for Fine Chemicals Production: Materials and Processes*; Springer: New York, **2010**.
[6] Mathur, N. K.; Williams, R. E. Organic Syntheses Using Polymeric Supports, Polymeric Reagents, and Polymeric Catalysts. *J. Macromol. Sci.-Rev. Macromol. Chem.* **1976**, *15*, 117–142. doi:10.1080/15321797608065776.
[7] Lehnert, W. Knoevenagel Kondensationen Mit $TiCl_4$/base-IV: Umsetzungen Von Aldehyden Und Ketonen Mit Phosphonoessigester Und Methylendiphosphonsäureestern. *Tetrahedron.* **1974**, *30*, 301–305. doi:10.1002/chin.197421307.

[8] Lehnert, W. Knoevenagel-Kondensationen Mit $TiCl_4$/base-VI. 3-Alkyliden- Und 3-Aryliden-2,4-Pentandione Aus Aldehyden Und Acetylaceton. *Synthesis.* **1974**, *9*, 667–669. doi:10.1055/s-1974-23400.

[9] Kishikawa, K.; Furusawa, A.; Kohmoto, S.; Yamamoto, M.; Kazutoshi, Y. K. Diastereoselective Hydrochlorination of Acrylylurea Derivatives Using Titanium Tetrachloride and Alcohol. Chelation-Controlled Michael Addition of Chloride and Intramolecular Proton Transfer to the.alpha.-Position. *J. Org. Chem.* **1993**, *58*, 7296–7299. doi:10.1021/jo00077a067.

[10] Odian, G. *Principles of Polymerization*, Fourth Ed.; John Wiley & Sons, INC Publication: New York, **2004**.

[11] Stellman, J. M. Encyclopedia of Occupational Health and Safety. **1998**.

[12] Allochio Filho, J. F.; Lemos, B. C.; de Souza, A. S.; Pinheiro, S.; Greco, S. J. Multicomponent Mannich Reactions: General Aspects, Methodologies and Applications. *Tetrahedron.* **2017**, *73*, 6977–7004. doi:10.1016/j.tet.2017.10.063.

[13] Wu, M.; Jing, H.; Chang, T. Synthesis of β-Amino Carbonyl Compounds via a Mannich Reaction Catalyzed by SalenZn Complex. *Catal. Commun.* **2007**, *8*, 2217–2221. doi:10.1016/j.catcom.2007.05.011.

[14] Zhang, C.; Dong, J.; Cheng, T.; Li, R. $Y(OTf)_3$-Catalyzed Novel Mannich Reaction of *N*-Alkoxycarbonylpyrroles, Formaldehyde and Primary Amine Hydrochlorides. *Tetrahedron Lett.* **2001**, *42*, 461–463. doi:10.1016/S0040-4039(00)01985-7.

[15] Shou, W.-G.; Yang, Y.-Y.; Wang, Y.-G. An Efficient Synthesis of β-Amino Esters via $Zn(OTf)_2$-Catalyzed Mannich-Type Reaction. *Tetrahedron Lett.* **2006**, *47*, 1845–1847. doi:10.1016/j.tetlet.2005.12.136.

[16] Kogayashi, S.; Araki, M.; Yasuda, M. One-Pot Synthesis of β-Amino Esters from Aldehydes Using Lanthanide Triflate as a Catalyst. *Tetrahedron Lett.* **1995**, *36*, 5773–5776. doi:10.1016/0040-4039(95)01096-Z.

[17] Pandey, G.; Singh, R. P.; Garg, A.; Singh, V. K. Synthesis of Mannich Type Products via a Three-Component Coupling Reaction. *Tetrahedron Lett.* **2005**, *46*, 2137–2140. doi:10.1016/j.tetlet.2005.01.118.

[18] Zhang, X.; Yin, S.; Qiu, R.; Xia, J.; Dai, W.; Yu, Z.; Au, C.-T.; Wong, W.-W. Synthesis and Structure of an Air-Stable Hypervalent Organobismuth (III) Perfluorooctanesulfonate and Its Use as High-Efficiency Catalyst for Mannich-Type Reactions in Water. *J. Organomet. Chem* **2009**, *694*, 3559–3564. doi:10.1016/j.jorganchem.2009.07.018.

[19] Loh, T.-P.; Liung, S. B. K. W.; Tan, K.-L.; Wei, L.-L. Three Component Synthesis of β-Amino Carbonyl Compounds Using Indium Trichloride-Catalyzed One-Pot Mannich-Type Reaction in Water. *Tetrahedron.* **2000**, *56*, 3227–3237. doi:10.1016/S0040-4020(00)00221-0.

[20] Wang, R.; Li, B.-G.; Huang, T.-K.; Shi, L.; Lu, X.-X. $NbCl_5$-Catalyzed One-Pot Mannich-Type Reaction: Three Component Synthesis of β-Amino Carbonyl Compounds. *Tetrahedron Lett.* **2007**, *48*, 2071–2073. doi:10.1016/j.tetlet.2007.01.142.

[21] Wang, L.; Han, J.; Sheng, J.; Tian, H.; Fan, Z. Rare Earth Perfluorooctanoate $[RE(PFO)_3]$ Catalyzed One-Pot Mannich Reaction: Three Component Synthesis of β-Amino Carbonyl Compounds. *Catal. Commun.* **2005**, *6*, 201–204. doi:10.1016/j.catcom.2004.12.009.

[22] Yang, Y.-Y.; Shou, W.-G.; Wang, Y.-G. Synthesis of β-Amino Carbonyl Compounds via a $Zn(OTf)_2$-Catalyzed Cascade Reaction of Anilines with Aromatic Aldehydes and Carbonyl Compounds. *Tetrahedron.* **2006**, *62*, 10079–10086. doi:10.1016/j.tet.2006.08.063.

[23] Ollevier, T.; Nadeau, E. Bismuth Triflate-Catalyzed Three-Component Mannich-Type Reaction. *J. Org. Chem.* **2004**, *69*, 9292–9295. doi:10.1021/jo048617c.

[24] Manabe, K.; Kobayashi, S. Mannich-Type Reactions of Aldehydes, Amines, and Ketones in a Colloidal Dispersion System Created by a Brønsted Acid-Surfactant-Combined Catalyst in Water. *Org. Lett.* **1999**, *1*, 1965–1967. doi:10.1021/ol991113u.

[25] Manabe, K.; Mori, Y.; Kobayashi, S. Three-Component Carbon–Carbon Bond-Forming Reactions Catalyzed by a Brønsted Acid–Surfactant-Combined Catalyst in Water. *Tetrahedron.* **2001**, *57*, 2537–2544. doi:10.1016/S0040-4020(01)00081-3.

[26] Azizi, N.; Torkiyan, L.; Saidi, M. R. Highly Efficient One-Pot Three-Component Mannich Reaction in Water Catalyzed by Heteropoly Acids. *Org. Lett.* **2006**, *8*, 2079–2082. doi:10.1021/ol060498v.

[27] Goswami, P.; Das, B. Adenine as Aminocatalyst for Green Synthesis of Diastereoselective Mannich Products in Aqueous Medium. *Tetrahedron Lett.* **2009**, *50*, 2384–2388. doi:10.1016/j.tetlet.2009.02.218.

[28] Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F. Amine-Catalyzed Direct Asymmetric Mannich-Type Reactions. *Tetrahedron Lett.* **2001**, *42*, 199–201. doi:10.1016/S0040-4039(00)01908-0.

[29] Kantam, M. L.; Rajasekhar, C. V.; Gopikrishna, G.; Reddy, K. R.; Choudary, B. M. Proline Catalyzed Two-Component, Three-Component and Self-Asymmetric Mannich Reactions Promoted by Ultrasonic Conditions. *Tetrahedron Lett.* **2006**, *47*, 5965–5967. doi:10.1016/j.tetlet.2006.06.042.

[30] Wu, H.; Chen, X.-M.; Wan, Y.; Ye, L.; Xin, H.-Q.; Xu, H.-H.; Yue, C.-H.; Pang, L.-L.; Ma, R.; Shi, D.-Q. Stereoselective Mannich Reactions Catalyzed by Tröger's Base Derivatives in Aqueous Media. *Tetrahedron Lett.* **2009**, *50*, 1062–1065. doi:10.1016/j.tetlet.2008.12.067.

[31] Alza, E.; RodrIguez-Escrich, C.; Sayalero, S.; Bastero, A.; M. A. Chem, P. A Solid-Supported Organocatalyst for Highly Stereoselective, Batch, and Continuous-Flow Mannich Reactions. *Chem Eur J.* **2009**, *15*, 10167–10172.

[32] Senapak, W.; Saeeng, R.; Sirion, U.; Acid-Ionic Polymer as Recyclable Catalyst for One-Pot Three-Component Mannich Reaction. *RSC Adv.* **2017**, *7*, 30380–30384. doi:10.1039/C7RA04834C.

[33] Zhao, G.; Jiang, T.; Gao, H.; Han, B.; Huang, J.; Sun, D.; Mannich Reaction Using Acidic Ionic Liquids as Catalysts and Solvents. *Green Chem.* **2004**, *6*, 75–77. doi:10.1039/b309700p.

[34] Sahoo, S.; Joseph, T.; Halligudi, S. B.; Mannich Reaction in Brönsted Acidic Ionic Liquid: A Facile Synthesis of *β*-Amino Carbonyl Compounds. *J. Mol. Catal. A: Chem.* **2006**, *244*, 179–182. doi:10.1016/j.molcata.2005.09.012.

[35] Dong, F.; Luo, J.; Zhou, X.-L.; Liu, Z.-L.; Mannich Reaction in Water Using Acidic Ionic Liquid as Recoverable and Reusable Catalyst. *Catal. Lett.* **2007**, *116*, 76–80. doi:10.1007/s10562-007-9095-8.

[36] Dong, F.; Zhenghao, F.; Zuliang, L.; Functionalized Ionic Liquid as the Recyclable Catalyst for Mannich-Type Reaction in Aqueous Media. *Catal. Commun.* **2009**, *10*, 1267–1270. doi:10.1016/j.catcom.2009.02.003.

[37] Wu, H.; Shen, Y.; Fan, L.-Y.; Wan, Y.; Zhang, P.; Chen, C.-F.; Wang, W.-X.; Stereoselective Synthesis of *β*-Amino Ketones via Direct Mannich-Type Reaction Catalyzed with Silica Sulfuric Acid. *Tetrahedron.* **2007**, *63*, 2404–2408. doi:10.1016/j.tet.2007.01.015.

[38] Li, Z.; Ma, X. L.; Liu, J.; Feng, X.; Tian, G.-Q.; Zhu, A. G.; Silica-Supported Aluminum Chloride: A Recyclable and Reusable Catalyst for One-Pot Three-Component Mannich-Type Reactions. *J. Mol. Catal. A Chem.* **2007**, *272*, 132–135. doi:10.1016/j.molcata.2007.03.029.

[39] Kidwai, M.; Mishra, N. K.; Bansal, V.; Kumar, A.; Mozumdar, S.; Novel One-Pot Cu-Nanoparticles-Catalyzed Mannich Reaction. *Tetrahedron Lett.* **2009**, *50*, 1355–1358. doi:10.1016/j.tetlet.2009.01.031.

[40] Zareyee, D.; Alizadeh, H.; One-Pot Three-Component Mannich Reaction in Water Catalyzed by Eco-Friendly, Hydrophobic and Recyclable Sulfonic Acid Based Nanosilica (SBA-15-Ph-PrSO_3H). *RSC Adv.* **2014**, *4*, 37941–37946. doi:10.1039/C4RA05842A.

[41] Rahmatpour, A.; Goodarzi, N.; Moazzez, M.; 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.* **2018**, *21*, 116–129. doi:10.1080/15685551.2018.1489698.

[42] Rahmatpour, A.; Polystyrene-Supported $GaCl_3$: A New, Highly Efficient and Recyclable Heterogeneous Lewis Acid Catalyst for Tetrahydropyranylation of Alcohols and Phenols. *Polyhedron.* **2012**, *44*, 66–71. doi:10.1016/j.poly.2012.06.063.

[43] Rahmatpour, A.; Polyvinylsulfonic Acid: An Efficient, Water-Soluble and Reusable Brønsted Acid Catalyst for the Three-Component Synthesisof 3,4-Dihydropyrimidin-2(1H)-Ones/Thiones in Water and Ethanol. *Catal. Lett.* **2012**, *142*, 1505–1511. doi:10.1007/s10562-012-0873-6.

[44] Rahmatpour, A.; Goodarzi, N.; Cross-Linked polystyrene-$TiCl_4$ Complex as a Reusable Lewis Acid Catalyst for Solvent-Free Knoevenagel Condensations of 1,3-Dicarbonyl Compounds with Aldehydes. *Catal. Commun.* **2019**, *124*, 24–31. doi:10.1016/j.catcom.2018.11.001.

[45] Deshmukh, P.; Padiya, K. J.; Salunkhe, M. M. Friedel–Crafts acylation reaction using polymer supported aluminium chloride. *J. Chem. Res (S).* **1999**, 9, 568–569. DOI: 10.1039/a808986h.

[46] Eftekhari-Sis, B.; Abdollahifar, A.; Hashemi, M. M.; Zirak, M. Stereoselective synthesis of β-Amino ketones via direct Mannich-type reactions, catalyzed with $ZrOCl_2{\cdot}8\,H_2O$ under solvent-free conditions. *Eur. J. Org. Chem.* **2006**, 5152–5157. DOI: 10.1002/ejoc.200600493.

[47] Lin, Y.; Huangshu, L.; Junhua, Z.; Xiujuan, X. The Mannich reaction between aromatic ketones, aromatic aldehydes and aromatic amines. *Synthesis.* **1991**, 9, 717–718. DOI: 10.1055/s-1991-26554.

[48] Li, J.; Peng, Y.; Song, G. Mannich reaction catalyzed by carboxyl-functionalized ionic liquid in aqueous media. Catal. Lett. **2005**, 102, 159–162. DOI: 10.1007/s10562-005-5849-3.

[49] Li, H.; Zeng, H.-Y.; Shao, H.-W. Bismuth(III) chloride-catalyzed one-pot Mannich reaction: three-component synthesis of β-amino carbonyl compounds. *Tetrahedron Lett.* **2009**, 50, 6858–6860. DOI: 10.1016/j.tetlet.2009.09.131.

[50] Bigdeli, M. A.; Nemati, F.; Mahdavinia, G. H. $HClO_4$–SiO_2 catalyzed stereoselective synthesis of β-amino ketones via a direct Mannich-type reaction. *Tetrahedron Lett.* **2007**, 48, 6801–6804. DOI: 10.1016/j.tetlet.2007.07.088.

[51] Chang, C.-T.; Liao, B.-S.; Liu, S.-T. Mannich-type reactions in a colloidal solution formed by sodium tetrakis(3,5-trifluoromethylphenyl)borate as a catalyst in water. *Tetrahedron Lett.* **2006**, 47, 9257–9259. DOI: 10.1016/j.tetlet.2006.10.125.

[52] Yi, W.-B.; Cai, C. Mannich-type reactions of aromatic aldehydes, anilines, and methyl ketones in fluorous biphase systems created by rare earth (III) perfluorooctane sulfonates catalysts in fluorous media. *J. Fluorine Chem.* **2006**, 127, 1515–1521. DOI: 10.1016/j.jfluchem.2006.07.009.

[53] Yue, C.- B.; Yi, T. F.; Zhu, C. B.; Liu, G. Mannich reaction catalyzed by a novel catalyst under solvent-free conditions. *Ind. Eng. Chem.* **2009**, 15, 653–656. DOI: 10.1016/j.jiec.2009.09.038.

[54] Wang, M.; Song, Z.-G.; Xin, W.; Zhao, S. $SnCl_2$-catalyzed three-component one-pot Mannich-type reaction: efficient synthesis of β-aminocarbonyl compounds. *Monatsh Chem.* **2009**, 140, 1205–1208. DOI: 10.1007/s00706-009-0163-1.

[55] Boumoud, B.; Zetchi, A.; Boumoud, T.; Debache, A. SiO_2-$OSbCl_2$ as highly effective and reusable heterogeneous catalyst for Mannich condensation in solvent or under solvent-Free conditions. *J. Chem. Pharm. Res.* **2012**, 4(5), 2517–2521.

[56] Iimura, S.; Nobutou, D.; Manabe, K.; Kobayashi, S. Mannich-type reactions in water using a hydrophobic polymer-supported sulfonic acid catalyst. *Chem. Commun.* **2003**, 14, 1644–1645. DOI: 10.1039/b304343f.