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# Polyvinylpolypyrrolidone-supported boron trifluoride: a high-loaded, polymer-supported Lewis acid for the Ritter reaction

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**Abstract** A Mild and efficient method for preparing amides by reaction of nitriles with benzhydrol and tertiary alcohols is described using polyvinylpolypyrrolidone-supported boron trifluoride. Selective amidation of benzhydrol in the presence of primary benzyl alcohols was also achieved.

**Keywords** Ritter reaction · Polyvinylpolypyrrolidone · Boron trifluoride · Nitriles · Amides

## Introduction

Boron trifluoride is widely used in organic syntheses as a Lewis acid, including Friedel-Crafts alkylation [1, 2] and acylation [3, 4] reactions, conversion of aldehydes and ketones in to gem-difluoro compounds [5], cation-assisted rearrangement reactions [6, 7], Diels-Alder reactions [8], polymerization, etc. [9, 10]. However, boron trifluoride is highly water sensitive, irritant, and has to be used in a carefully dried apparatus. Furthermore, all work must be carried out in an efficient fume hood, and its recovery from the reaction mixture results in a significant source of waste, which on an industrial scale is environmentally unacceptable.

The Ritter reaction makes possible the conversion of a group, capable of giving a relatively stable carbonium ion, to a substituted amide by reaction with a nitrile in the presence of a strong acid [11-13]. The classical method,

M. M. Lakouraj (⊠) · M. Mokhtary Department of Organic-Polymer Chemistry, Faculty of Chemistry, Mazandaran University, Babolsar 47416, Iran e-mail: lakouraj@umz.ac.ir which utilizes an excess amount of concentrated sulfuric acid, is generally suitable for tertiary alcohols, but this strongly acidic medium limits its use, especially for acidsensitive substrates. Therefore, several modifications have been attempted to improve Ritter reaction conditions. Some alternative reagents used for this purpose are  $Ph_2C^+ClSb^-Cl_6$  [14],  $NO_2^+BF_4^-$  [15], NOPF\_6 [16],  $(CF_3SO_2)_2O$  [17],  $FeCl_3\cdot 6H_2O$  [18],  $BF_3$ - $Et_2O$  [19],  $Fe^{3+}$ -Montmorillonite [20], Mg(HSO\_4)\_2 [21], NHPI-CAN [22], *t*-butylacetate [23], HCO\_2H [24], Bi(OTf)\_3 [25], 7-Tetrachlorobenzo[d][1,2,3,]dioxoborol-2-ol [26], heteropolyacid [27], CeCl\_3·7H\_2O/AcCl [28], and P\_2O\_5/SiO\_2 [29].

However, many of these methods suffer from at least one of the following disadvantage: unavailability of the reagent, vigorous reaction conditions, strong protic and aqueous media, reagent high cost and toxicity, tedious workup procedures, unsatisfactory yields, long reaction time, instability, and hygroscopic nature of the reagent. On the other hand, catalyst recovery presents some unique advantages, such as waste reduction, lower cost, simple product isolation, energy savings, and environmental compatibility in chemical production both in laboratory and industrial processes.

Therefore, substantial investigations have been performed to introduce novel supported catalysts and chemical reagents. These include dispersing catalysts on inorganic beds such as metal oxide, alumina, silica, and zeolite. However, the supported catalyst becomes part of the waste stream after a few reaction cycles due to hydrolysis and leaching of the active species. In addition, several examples of polymer-supported catalysts are also reported in the literature [30].

There is a number of advantages in using polymersupported catalysts over conventional catalysis. The reactions can be performed under mild conditions, and product purification is simplified because of the use of an insoluble solid support. Many reactions can be carried out cleanly, rapidly, and in high yields. Polymer-supported catalysts can also be recycled after use. However, mainly, the polystyrene-based polymer-bound Lewis acid catalysts show relatively low activity, and the activity of the catalyst decreases due to insufficient stability of the aromatic ring of the polymer and slow diffusion of substrate into the network. Furthermore, the actual loading is limited by Lewis-acid-catalyzed cross linking of chloromethyl groups within the polystyrene-based resin. One of the most effective procedures to enhance the maximal loading of the carrier material is obtained by using low molecular weight functional monomers [31]. Poly(vinylpyrrolidone) is a blood plasma extender that can act as carrier for a variety of compounds in the bloodstream and has been used as a retardant for drugs and to eliminate toxins [32]. It displays a strong binding affinity toward small molecules, and its iodine complex, povidone-iodine, is widely used as an antiinfective agent in clinical treatment [33].

To develop a high-loading polymer-supported catalyst that can offer catalyst recoverability and also maintain long-term stability and activity, and in connection with our interest in design and application of functionalized polymers, we introduce here the polymeric Lewis-acid catalyst polyvinylpolypyrrolidone-supported boron trifluoride (PVPP-BF<sub>3</sub>). It can be used as a stable bench-top catalyst for selective amidation of benzhydrol and tertiary alcohols with nitriles. In contrast to boron trifluoride, which is extremely moisture sensitive, this reagent is not hygroscopic and retains its activity after several months of storage. Interestingly, this reagent not only gives good product yields, but PVPP-BF<sub>3</sub> is also easily regenerated and can be reused several times (Scheme 1).

 $R-OH + R'-CN \xrightarrow{PVPP-BF_3} R-NHCO-R'$   $R = (Ph)_2CH, (CH_3)_3C, PhCH_2(CH_3)_2C, adamantane$   $R' = Ar, vinyl, CICH_2, CH_3$ Scheme 1

## **Results and discussion**

In this study, PVPP- $BF_3$  is obtained by simple complexation of boron trifluoride with the cross-linked PVPP(Fig. 1). The use of linear polyvinylpyrrolidone was not satisfactory for complexation with boron trifluoride due to formation of a sticky gum. **Fig. 1** The chemical structure of polyvinylpolypyrrolidone-supported boron trifluoride



Characterization of the Lewis-acid sites present on the polymer was performed by recording the Fourier transform infrared spectroscopy (FT-IR) spectrum of PVPP-BF<sub>3</sub>, which shows a strong broad absorption at 1,000–1,200 cm<sup>-1</sup> for the BF bonds and a weak absorption at 1,654 cm<sup>-1</sup> corresponds to the unreacted amide group on the backbone (Fig. 2). The capacity of the reagent was determined by titration and found to be 10 mmol/g, whereas its silica-supported analogue has a loading capacity of less than 4 mmol/g [34, 35].

The catalytic activity of PVPP-BF<sub>3</sub> was tested using the reaction of benzhydrol with acetonitrile (Table 1). Low boiling nitriles could be used both as solvent and substrate. Reactions with high-boiling or solid nitriles could be performed in 1, 2-dichloroethane as the solvent under reflux condition. According to the FT-IR of the recycled catalyst and titration analysis, the acidic sites remain unchanged. But in reuse, a lower conversion is observed after three cycles relative to the freshly prepared catalyst. A variety of



**Fig. 2** The Fourier transform infrared spectroscopy (FT-IR) spectrum of polyvinylpolypyrrolidone (PVPP) and polyvinylpolypyrrolidone-supported boron trifluoride (PVPP-BF<sub>3</sub>) complex

Alcohols	Product <sup>a</sup>	Time/h	Yield/% <sup>b</sup>	M.p./°C (Ref.)
Ph <sub>2</sub> CHOH	1 MeCONHCHPh <sub>2</sub>	2	88	145–147 (144–6) [20]
Ph <sub>2</sub> CHOH	2 PhCONHCHPh <sub>2</sub>	2.5	75	168–169 (170–1) [20]
Ph <sub>2</sub> CHOH	<b>3</b> <i>p</i> - <i>Me</i> C <sub>6</sub> H <sub>4</sub> CONHCH <i>Ph</i> <sub>2</sub>	3	90	174–176 (176–7) [24]
Ph <sub>2</sub> CHOH	4 <i>m</i> -MeC <sub>6</sub> H <sub>4</sub> CONHCHPh <sub>2</sub>	3	70	151–154
Ph <sub>2</sub> CHOH	<b>5</b> <i>o-Me</i> C <sub>6</sub> H <sub>4</sub> CONHCHPh <sub>2</sub>	3	68	177–179
Ph <sub>2</sub> CHOH	<b>6</b> <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CONHCH <i>Ph</i> <sub>2</sub>	3	65	158–160
Ph <sub>2</sub> CHOH	7 ClCH <sub>2</sub> CONHPh <sub>2</sub>	4	65	126–127 (125–6) [20]
Ph <sub>2</sub> CHOH	8 CH <sub>2</sub> =CHCONHCHPh <sub>2</sub>	3	55	179–180 (178–9) [24]
(Me) <sub>3</sub> COH	<b>9</b> $Ph$ CONHC( $Me$ ) <sub>3</sub>	4	45	133–135 (133–4) [20]
(Me) <sub>3</sub> COH	<b>10</b> <i>p</i> - <i>Me</i> C <sub>6</sub> H <sub>4</sub> CONHC( <i>Me</i> ) <sub>3</sub>	4	40	117–118 [23]
$PhCH_2C(Me)_2OH$	11 PhCONHC(Me) <sub>2</sub> CH <sub>2</sub> Ph	4	40	102–103
1-Admantanol	12 PhCONH-ad	4	68	154–156
1-Admantanol	13 MeCONH-ad	4	60	150–151 (148–9) [14]
	Alcohols $Ph_2$ CHOH $Ph_2$ CHOH $Ph_2$ CHOH $Ph_2$ CHOH $Ph_2$ CHOH $Ph_2$ CHOH $Ph_2$ CHOH $Ph_2$ CHOH $Ph_2$ CHOH $(Me)_3$ COH $(Me)_3$ COH $Ph$ CH $_2$ C( $Me)_2$ OH 1-Admantanol 1-Admantanol	AlcoholsProducta $Ph_2$ CHOH1 $Me$ CONHCH $Ph_2$ $Ph_2$ CHOH2 $Ph$ CONHCH $Ph_2$ $Ph_2$ CHOH3 $p$ - $Me$ C <sub>6</sub> H <sub>4</sub> CONHCH $Ph_2$ $Ph_2$ CHOH4 $m$ - $Me$ C <sub>6</sub> H <sub>4</sub> CONHCH $Ph_2$ $Ph_2$ CHOH5 $o$ - $Me$ C <sub>6</sub> H <sub>4</sub> CONHCH $Ph_2$ $Ph_2$ CHOH6 $p$ -CIC <sub>6</sub> H <sub>4</sub> CDONHCH $Ph_2$ $Ph_2$ CHOH6 $p$ -CIC <sub>6</sub> H <sub>4</sub> CDONHCH $Ph_2$ $Ph_2$ CHOH7 CICH <sub>2</sub> CONH $Ph_2$ $Ph_2$ CHOH8 CH <sub>2</sub> =CHCONHCH $Ph_2$ $(Me)_3$ COH9 $Ph$ CONHC( $Me)_3$ $(Me)_3$ COH10 $p$ - $Me$ C <sub>6</sub> H <sub>4</sub> CONHC( $Me)_3$ $Ph$ CH <sub>2</sub> C( $Me)_2$ OH11 $Ph$ CONHC( $Me)_2$ CH <sub>2</sub> $Ph$ 1-Admantanol12 $Ph$ CONH-ad1-Admantanol13 $Me$ CONH-ad	Alcohols Product <sup>a</sup> Time/h $Ph_2$ CHOH 1 $Me$ CONHCH $Ph_2$ 2 $Ph_2$ CHOH 2 $Ph$ CONHCH $Ph_2$ 2.5 $Ph_2$ CHOH 3 $p$ - $Me$ C <sub>6</sub> H <sub>4</sub> CONHCH $Ph_2$ 3 $Ph_2$ CHOH 4 $m$ - $Me$ C <sub>6</sub> H <sub>4</sub> CONHCH $Ph_2$ 3 $Ph_2$ CHOH 5 $o$ - $Me$ C <sub>6</sub> H <sub>4</sub> CONHCH $Ph_2$ 3 $Ph_2$ CHOH 6 $p$ -CIC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CONHCH $Ph_2$ 3 $Ph_2$ CHOH 6 $p$ -CIC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CONHCH $Ph_2$ 3 $Ph_2$ CHOH 8 CH <sub>2</sub> =CHCONHCH $Ph_2$ 3 $Ph_2$ CHOH 9 $Ph$ CONHC( $Me$ ) <sub>3</sub> 4 $Ph_2$ CHOH 10 $p$ - $Me$ C <sub>6</sub> H <sub>4</sub> CONHC( $Me$ ) <sub>3</sub> 4 $Ph_2$ CHOH 11 $Ph$ CONHC( $Me$ ) <sub>2</sub> CH <sub>2</sub> $Ph$ 4 $Ph$ CH <sub>2</sub> C( $Me$ ) <sub>2</sub> OH 11 $Ph$ CONHC( $Me$ ) <sub>2</sub> CH <sub>2</sub> $Ph$ 4 $1$ -Admantanol 12 $Ph$ CONH-ad 4	AlcoholsProductaTime/hYield/%b $Ph_2$ CHOH1 $Me$ CONHCH $Ph_2$ 288 $Ph_2$ CHOH2 $Ph$ CONHCH $Ph_2$ 2.575 $Ph_2$ CHOH3 $p-MeC_6H_4$ CONHCH $Ph_2$ 390 $Ph_2$ CHOH4 $m-MeC_6H_4$ CONHCH $Ph_2$ 370 $Ph_2$ CHOH5 $o-MeC_6H_4$ CONHCH $Ph_2$ 368 $Ph_2$ CHOH6 $p-ClC_6H_4CH_2CONHCHPh_2$ 365 $Ph_2$ CHOH6 $p-ClC_6H_4CH_2CONHCHPh_2$ 355 $Ph_2$ CHOH7 ClCH_2CONH $Ph_2$ 465 $Ph_2$ CHOH8 CH_2=CHCONHCH $Ph_2$ 355 $(Me)_3$ COH9 $Ph$ CONHC $(Me)_3$ 445 $(Me)_3$ COH10 $p-MeC_6H_4$ CONHC $(Me)_3$ 440 $PhCH_2C(Me)_2$ OH11 $Ph$ CONHC $(Me)_2$ CH $_2Ph$ 4681-Admantanol12 $Ph$ CONH-ad460

Table 1 Amidation of benzhydrol and tertiary alcohols with nitriles using polyvinylpolypyrrolidone-supported boron trifluoride (PVPP-BF<sub>3</sub>)

<sup>a</sup> All the products were characterized by infrared (IR), <sup>1</sup>H NMR spectra and comparison with authentic samples

<sup>b</sup> All yields refer to isolated products

*N*-benzhydrylamides was prepared from benzhydrol to the corresponding nitriles in the presence of a catalytic amount of PVPP-BF<sub>3</sub> in good yields (Table 1, entries 1–8). Alifatic tertiary alcohols were converted to the corresponding amides in moderate yields (Table 1, entries 9–13). Primary benzylic alcohols do not undergo amidation with nitriles under the same condition, and in some cases only afforded a low yield of products. Attempts for amidation of primary and secondary saturated alcohols were unsuccessful. It is worth mentioning that the corresponding amide in each case was isolated by simple filtration of the catalyst followed by crystallization from the crude filtrate.

Additionally, the reaction's chemoselectivity was evaluated via competitive PVPP-BF<sub>3</sub>-catalyzed Ritter reaction of equimolar amounts of benzhydrol and *p*-chlorobenzyl alcohol in acetonitrile under reflux conditions. It was found that benzhydrol reacted with acetonitrile to give the corresponding amide in high yield, whereas *p*-chlorobenzyl alcohol remained unchanged (Fig. 3).

In conclusion, we synthesized a novel form of supported boron trifluoride that is stable, nonhygroscopic, easy to prepare and handle, shows a high loading of Lewis acid, and represents effective catalytic activity for the selective amidation of benzhydroles and *tert*-butyl alcohols with nitriles.



Fig. 3 Competitive amidation of benzhydrol versus *p*-chlorobenzyl alcohol

## Experimental

PVPP was purchased from Fluka. Other chemicals were purchased from Merck Chemicals. Melting points were recorded on an electrothermal melting-point apparatus. Nuclear magnetic resonance (NMR) spectra were recorded in CDCl<sub>3</sub>, with TMS as an internal standard on a Bruker advance DRX 500 MHz spectrometer. IR spectra were determined on an SP-1100, P-UV-Com instrument. Product purity determination was accomplished by thin-layer chromatography (TLC) on silica gel polygram SIL G/UV 254 plates. Products were separated by simple filtration and identified by comparison IR and <sup>1</sup>H NMR spectra with those reported for authentic samples.

## *Polyvinylpolypyrrolidone–boron trifluoride complex* (*PVPP-BF*<sub>3</sub>)

To a suspension of 3 g PVPP in 25 cm<sup>3</sup> CH<sub>2</sub>Cl<sub>2</sub>, a solution of 5 cm<sup>3</sup> BF<sub>3</sub>·OEt<sub>2</sub> in 15 cm<sup>3</sup> CH<sub>2</sub>Cl<sub>2</sub> was added dropwise and the mixture stirred for 1 h at room temperature. The resulting resin was filtered and washed with  $2 \times 10$  cm<sup>3</sup> CH<sub>2</sub>Cl<sub>2</sub> and dried in a vacuum desiccator to give a stable and nonhygroscopic powder.

## Ritter reaction of benzhydrol: general procedure

A solution of 1 mmol benzhydrol and 2 mmol nitrile in 5 cm<sup>3</sup> 1,2-dichloroethane was prepared; 3 mmol PVPP-BF<sub>3</sub> was added to the solution, and the reaction mixture was stirred for 2–4 h under reflux condition until TLC analysis showed that no benzhydrol remained. The reaction mixture was filtered and washed with  $2 \times 5$  cm<sup>3</sup> CH<sub>2</sub>Cl<sub>2</sub>,

and the solvent was evaporated on a rotatory evaporator under diminished pressure. The solid residue was recrystalized from ethanol (96%) to afford pure crystals of the proper amides in 40–90% yields.

#### N-Benzhydryl-3-methylbenzamide (4, $C_{21}H_{19}NO$ )

Yield 70%; m. p.: 151–154°C. IR (KBr):  $\bar{\nu} = 3,318; 1,636;$ 1,603; 1,541; 1,503; 1,496; 752; 702 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 2.44$  (s, 3H); 6.49 (d, J = 7.8 Hz, 1H); 6.68 (d, J = 7.8 Hz, 1H); 7.3–7.68 (m, 14H) ppm.

#### N-Benzhydryl-2-methylbenzamide (5, $C_{21}H_{19}NO$ )

Yield 68%; m. p.: 177–179°C. IR (KBr):  $\bar{v} = 3,297; 1,649;$ 1,525; 1,503; 1,494; 752; 702 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 2.48$  (s, 3H); 6.38 (d, J = 7.8 Hz, 1H); 6.49 (d, J = 8 Hz, 1H); 7.25–7.47(m, 14H) ppm.

## *N-Benzhydryl-2-(4-chlorophenyl)acetamide* (**6**, *C*<sub>21</sub>*H*<sub>18</sub>*NOCl*)

Yield 65%; m. p.: 158–160°C. IR (KBr):  $\bar{\nu} = 3,307; 1,649;$ 1,541; 1,503; 1,489; 772; 693 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 3.62$  (s, 2H); 6.11 (d, J = 10 Hz, 1H); 6.27 (d, J = 8 Hz, 1H); 7.15–7.36(m, 14H) ppm.

## N-(1,1-Dimethyl-2-phenylethyl)benzamide

 $(11, C_{17}H_{19}NO)$ 

Yield 40%; m. p.: 102–103°C; IR (KBr):  $\bar{\nu} = 3,327; 2,978;$ 1,638; 1,542; 1,222; 735 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 1.50$  (s, 6H); 5.22 (s, 2H); 5.74 (br, 1H); 7.22–7.67 (m, 10H) ppm.

#### N-(1-Adamantyl)benzamide (12, $C_{17}H_{21}NO$ )

Yield 68%; m.p.: 154–156°C; IR (KBr):  $\bar{\nu} = 3,332; 2,912;$ 2,852; 1,633; 1,537; 1,451; 1,282; 716; 692 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta = 1.73-1.79$ (br, 6H); 2.1(br, 9H); 5.85 (br, 1H); 7.3–7.76 (m, 5H) ppm.

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