Convenient Synthesis of Benzamides Mediated by Poly(4-vinylpyridine)-Supported Benzoyl Chloride

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ABSTRACT: The use of polymeric reagents simplifies the routine acylation of amines because it eliminates traditional purification. In this article, the use of readily available crosslinked poly(4-vinylpyridine)-supported benzoyl chloride as an acylating agent of amines in the presence of K_2CO_3 in *n*-hexane is described. The product was readily obtained by the filtration and evaporation of the solvent. The spent polymeric reagent could be regenerated and reused. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 119: 2345–2349, 2011

Key words: ion exchangers; networks; resins; supports; synthesis

INTRODUCTION

Although polymeric reagents and scavengers have been used in organic synthesis for decades, the development of combinatorial and parallel high-throughput synthesis techniques has brought this class of reagents to a wider attention. The first compound collections were based on peptides and oligonucleotides, which were assembled stepwise on a solid support[1] according to the concept developed by Merrifield.[2] Polymer-supported reagents, especially anion-exchange resins, have been widely applied in organic syntheses.[3–14] These polymeric reagents are generally used in single-step reactions. Their main advantage over monomeric reagents is their insolubility in the reaction medium and, consequently, easier workup by a simple filtration. The reactions can often be driven to completion with an excess of initial reagents without the fear of separating the unspent reagent from the desired products. The spent polymeric reagents can usually be removed quantitatively and regenerated. In addition, anions bounded to the macroporous resin have the advantage that they often react successfully in nonpolar solvents.

Amide synthesis is a widely used reaction in organic syntheses, especially as intermediates for drugs and pharmaceuticals, azo and sulfur dyes, fine chemicals, and also, an additive for hydrogen peroxide, photographic chemicals, and antioxidants.[15] The acylation of amines is usually performed with acid chlorides or anhydrides as acylating agents in the presence of stoichiometric amounts of amine, such as pyridine derivatives, 4-(dimethylamino) pyridine or 4-pyrrolidonopyridine,[16,17] tertiary amines,[17] tributylphosphine,[18] and Lewis acids, such as lithium chloride,[19] zinc chloride,[20] and cobalt chloride.[21]

Although numerous applications of solid-supported reagents and scavengers are reported in literature,[3–14] there have only been a few reports on amide synthesis.[22–28] Among them have been the acylation of amines with polymer-supported *N*-alkyl-2-chloropyridinium triflate,[22] resin-bound 4-phenyl-1,2-dihydroquinoline,[23] polymer-supported carbodiimide,[24,25] crosslinked polystyrene-supported oximino esters,[26] polymer-supported pyrimidine,[27] polymer-bound cyclohexane-1,3-dione resin,[28] and poly(4-vinylpyridine).[29] Unfortunately, each of the reported methods for the synthesis of amides suffered from at least one of the following disadvantages: (1) the yields of the reactions were low, (2) the reaction had to be carried out in the presence of a phase-transfer catalyst, (3) the reaction mixture had to be acidified or the reaction had to be catalyzed by a base such as pyridine, and (4) the work-up products needed several steps, especially in the latest method of the synthesis of amides by poly(4-vinylpyridine), which required the addition of pentaethylenehexamine and 1,4-phenylenediisocyanate to remove excess acid chloride or an excess of amine. Polymer-supported benzoyl chloride overcomes most of the aforementioned disadvantages.

In continuing of our studies of the application of crosslinked poly(4-vinylpyridine) in organic synthesis,[9–14,30,31] herein, we report a novel, clean, and

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simple method in which amines reacted with benzoyl chloride in the presence of excess poly(4-vinylpyridine) crosslinked with 2% divinylbenzene and K_2CO_3 in a nonaqueous solvent such as *n*-hexane.

EXPERIMENTAL

Chemicals

Chemicals were purchased from Fluka, Merck (Buchs, Switzerland), and Aldrich (Milwaukee, WI) chemical companies. The progress of the reaction was followed by thin-layer chromatography with silica gel PolyGram SIL G/UV 254 plates. All products were characterized by the comparison of their Fourier transform infrared (FTIR) and ^{1}H-NMR spectra and physical data with those of known samples, and all yields refer to the isolated pure products. FTIR and ^{1}H-NMR spectra were run on a Bruker Equinox (Germany) (model 55) and a Jeol-JNM-EX 90-MHz spectrophotometer, respectively.

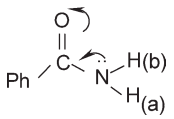
General procedure for the preparation of the amides

To a suspension of crosslinked poly(4-vinylpyridine) (1.15 g, 6 equiv) in *n*-hexane (10 mL) was added freshly distilled benzoyl chloride (281 mg, 2 mmol). The mixture was stirred at room temperature or at 50°C for 30 min; then, 2 mmol of amine and 376 mg (2 mmol) of K_2CO_3 were added, and stirring continued for 1–24 h at room temperature or for 0.5–24 h at 50°C. The polymeric support was recovered by filtration, washed with 5 mL of *n*-hexane and 5 mL of ethanol, and regenerated by successive treatment with a 10% solution of sodium hydroxide; the samples were washed twice with distilled water and dried in a vacuum oven at 40°C for 24 h. Evaporation of the solvent provided pure benzamide or N-substituted benzamides in high yields (80–97% at room temperature and 81–97% at 50°C), but when the secondary amine was used, the reaction equilibrium was not complete conversion to the product, and chromatography on silica gel (eluent = 10/90 acetone/*n*-hexane) provided highly pure products in low yields (10–15%).

Preparation of *N*-phenyl benzoamide at room temperature: A typical procedure

To a suspension of crosslinked poly(4-vinylpyridine) (1.15 g, 6 equiv) in *n*-hexane (10 mL) was added freshly distilled benzoyl chloride (281 mg, 2 mmol). The mixture was stirred at room temperature for 30 min; then, 212 mg (2 mmol) of aniline and 376 mg (2 mmol) of K_2CO_3 were added, and stirring continued for 8 h. The polymeric support was recovered by filtration and washed with 5 mL of *n*-hexane and 5 mL of ethanol. The evaporation of the solvents provided pure product in a high isolated yield (355 mg, 90%; mp = 162–163; ref. 32, 162°C). Selected spectra data for some of the benzamides prepared are given later, and selected FTIR and ^{1}H-NMR spectra of some of the benzamides prepared are shown in Figure 1.

Benzamide



FTIR (KBr, ν, cm^{-1}): 3390 (NH_2, asymmetric); 3180 (NH_2, symmetric); 2925–3000 (C—H, aromatic); 1649 (C=O); 1599, 1577 (C=C, aromatic); 634, 773 (monosubstituted). ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.5–7.8 (5H, m, aromatic), 7.4 [1H, NH (a)], 8 [1H, NH (b)].

N-Phenylbenzamide or benzanilide

FTIR (KBr, ν, cm^{-1}): 3344 (N—H); 3052 (C—H); 1655 (C=O); 1599, 1578, 1530, 1438 (C=C, aromatic); 750, 690 (monosubstituted). ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.1–8.1 (10H, m, aromatic), 10.25 (1H, br, NH).

4′-Methoxy benzanilide

FTIR (KBr, ν, cm^{-1}): 3331 (N—H); 3050 (C—H, aromatic); 2838, 2962.5 (C—H aliphatic); 1647 (C=O); 1516, 1578, 1515, 1469 (C=C, aromatic); 1270, 1249 (C—O); 1108, 1175 (C—N); 793, 692 (monosubstituted). ^{1}H-NMR ($CDCl_3$, δ, ppm): 3.8 ($O—CH_3$), 6.8–7.9 (9H, m, aromatic), 10.2 (1H, br, NH).

4′-Acetyl benzanilide

FTIR (KBr, ν, cm^{-1}): 3352 (N—H); 3050 (C—H, aromatic); 2838, 2962.5 (C—H aliphatic); 1674, 1652 (C=O); 1597, 1522, 1486 (C=C, aromatic); 1274, 1182 (C—N); 829, 717 (monosubstituted). ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.6 (CH_3), 7.3–8.15 (9H, m, aromatic), 10.1 (1H, br, NH).

4′-Bromobenzanilide

FTIR (KBr, ν, cm^{-1}): 3333 (N—H); 3000–3050 (C—H, aromatic); 2850, 2960 (C—H aliphatic); 1648 (C=O); 1592, 1578, 1521, 1491 (C=C, aromatic); 1258, 1179 (C—N); 820, 794 (monosubstituted). ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.3–7.9 (9H, m, aromatic), 10.25 (1H, br, NH).

RESULTS AND DISCUSSION

Poly(4-vinylpyridine)-supported benzoyl chloride (II) was prepared according to our previously reported

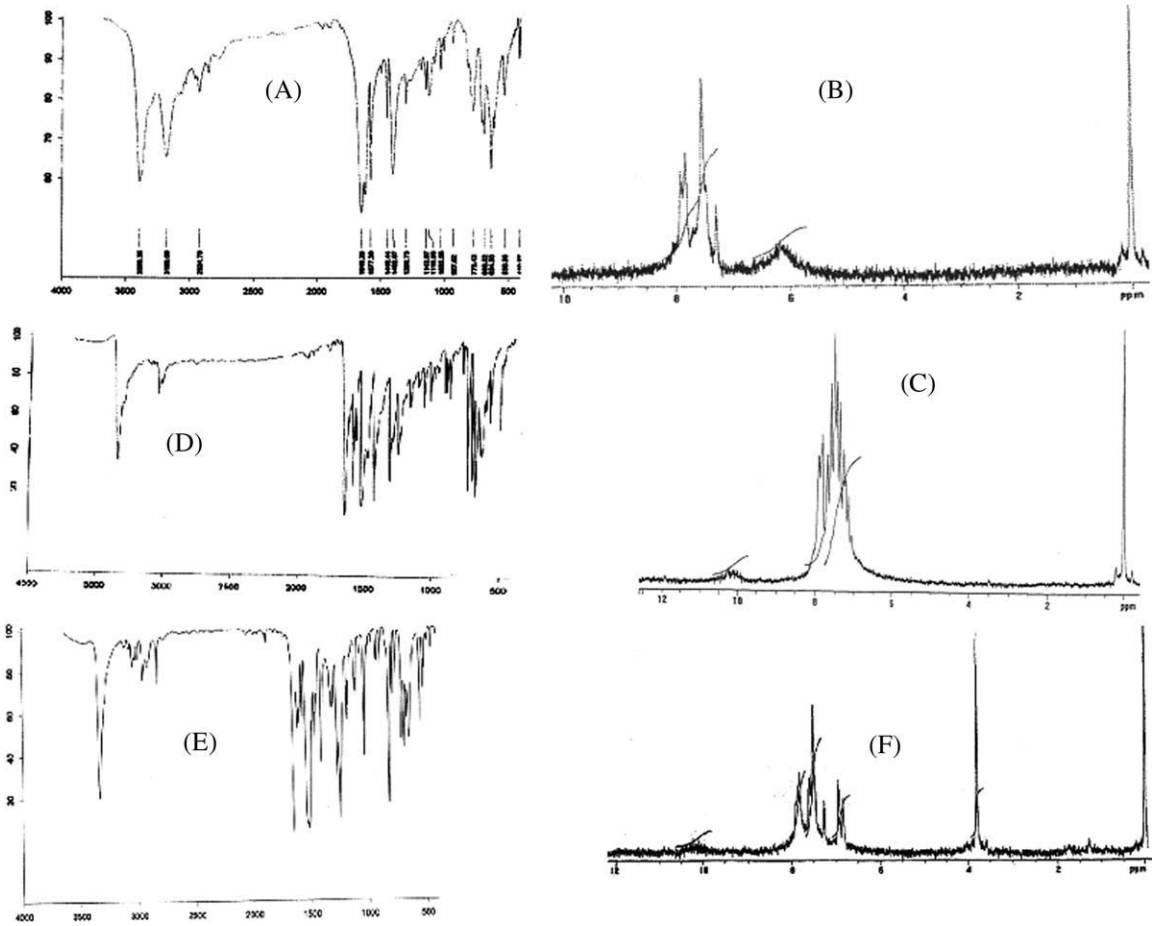


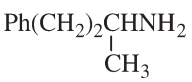
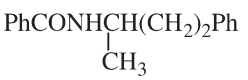
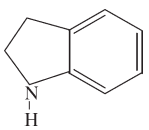
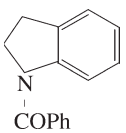
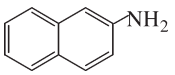
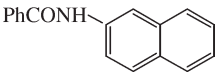
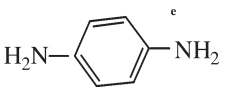
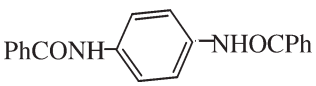
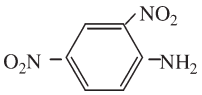
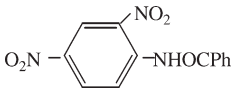
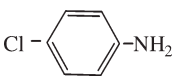
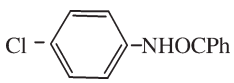
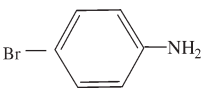
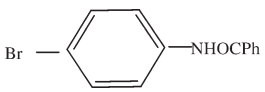
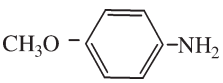
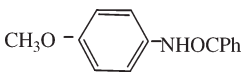
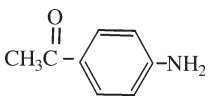
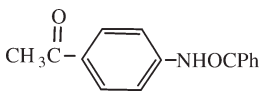
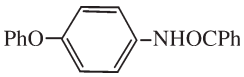
Figure 1 FTIR spectra of (A) benzamide, (D) benzanilide, and (E) *p*-methoxybenzanilide and ^{1}H-NMR spectra of (B) benzamide, (C) benzanilide, and (F) *p*-methoxybenzanilide.

procedure[31] and analyzed by FTIR spectroscopy. In this respect, the appearance of strong peaks at 1635 and 1710 cm^{-1} indicated the formation of poly(*N*-benzoyl-4-vinylpyridinium) chloride by acylation of the pyridine pendent group of the polymer with benzoyl chloride. This result was in accordance with spectroscopic observation of the acyl pyridinium ion by Fersht and Jencks.[33]

Previously, this polymeric reagent was used as an acylating reagent for the synthesis of esters;[31] herein, we report a clean and simple method, in which amine acylation occurred by a typical transacylation pathway. This method is an efficient procedure for conversion of ammonia or aliphatic or aromatic primary or secondary amines to the corresponding benzamides under mild and heterogeneous conditions at room temperature or at 50°C (with increasing temperature, the reaction time decreased); (Table I) and takes place with good-to-excellent yields (10–97%; Table I). *n*-Hexane was the best solvent among other nonpolar organic solvents.

A number of available amines, such as ammonia solution, primary or secondary amines, aniline, or derivatives of aniline, 2-aminonaphthaline, and indoline, were used for synthesis of the corresponding benzamides with poly(4-vinylpyridine)-supported benzoyl chloride (II) in the presence of K_2CO_3 in *n*-hexane. Although the polymeric reagent acted as a base and trapped the hydrochloric acid generated in the reaction by the excess of polymer, which displaced the equilibrium toward the amide formation, in the presence of K_2CO_3, the reaction took place faster, probably because the reagent acted as a base and, with proton abstraction from amines, increased the nucleophilicity of the amines, and the amide bond formation was faster. The amides were obtained simply by the filtration and evaporation of the solvent, and the results and reaction conditions are given in Table I. To establish a simple work-up procedure, we applied an excess of polymer (6 equiv). The polymer acylation occurred with benzoyl chloride [eq. (1) in Scheme 1], and the amidation step proceeded by the nucleophilic displacement of the amines in the presence of K_2CO_3 [eq. (2) in Scheme 1]. Among the evidence that supported this mechanism (transacylation pathway) was the appearance of strong peaks at 1635 and 1710 cm^{-1} in the FTIR spectrum of poly(*N*-benzoyl-4-vinylpyridinium) chloride

TABLE I
Preparation of Benzamides from Amines with Poly(4-vinylpyridine)-Supported Benzoyl Chloride and K_2CO_3

Entry	Substrate	Product[a]	Reaction time (h)[c]	Yield (%)[b,c]
1	NH_3	$PhCONH_2$	1 (0.5)	95 (95)
2	$PhNH_2$	PhCONHPh	8 (5)	90 (92)
3	$PhCH_2NH_2$	$PhCONHCH_2Ph$	1.5 (1.5)	97 (98)
4	$PhNHNH_2$	PhCONHNHPh	6.5 (5)	89 (91)
5			7 (2)	89 (90)
6	$NH_2(CH_2)_2NH_2$[e]	$PhCONH(CH_2)_2NHCOPh$	4.5 (1.5)	96 (97)
7	$(PhCH_2)_2NH$	$PhCON(CH_2Ph)_2$	24 (24)	10[d] (15[d])
8	Ph_2NH	$PhCONPh_2$	24 (24)	5[d] (15[d])
9			24 (24)	10[d] (12[d])
10			12 (9.5)	85 (89)
11			18 (16)	90 (93)
12			24 (24)	0.0 (0.0)
13			11 (10)	82 (82)
14			10 (9)	87 (86)
15			9 (6)	91 (92)
16			16 (15)	80 (81)
17			7 (3.5)	95 (96)

The reactions were performed in *n*-hexane with 6 equiv of crosslinked poly(4-vinylpyridine), PhCOCl (1 mmol), amine (1 mmol), and K_2CO_3 (1 mmol).

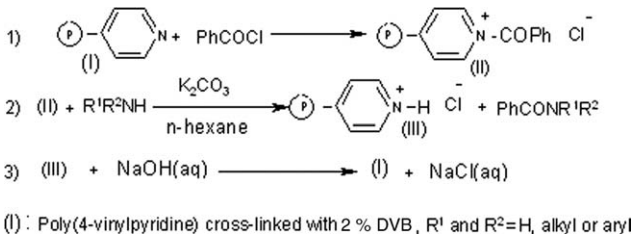
[a] The structures were confirmed through comparisons of the boiling points and IR and NMR spectra with those of authentic specimens.

[b] Isolated yields.

[c] Values in parentheses correspond to reactions taking place at 50°C.

[d] The equilibrium reaction was not completely converted to the product, and chromatography on silica gel (eluent = 10/90 acetone/*n*-hexane) provided highly pure products.

[e] The reaction was performed in *n*-hexane with 6 equiv of crosslinked poly(4-vinylpyridine), PhCOCl (2 mmol), amine (1 mmol), and K_2CO_3 (2 mmol).



Scheme 1 Mechanism of acyl transfer and regeneration of the polymer.

and the spectroscopic analysis of the acyl pyridinium ion.[33] The spent polymeric reagent was regenerated by stirring with a 10% solution of sodium hydroxide [eq. (3) in Scheme 1].

The relative reactivity of the amines toward amidation was in the following order, $NH_3 > 1° > 2°$ (entries 1, 3, 5, and 7–9 in Table I), and Aliphatic amine > Aromatic amine (entries 2, 3, and 5 in Table I), which was in agreement with a nucleophilic substitution process. This may have been because the larger molecules had more difficulty in gaining access to the active sites in the polymer. Also, withdrawing groups, such as $-COCH_3$, $-NO_2$, or halogen in the *p*-position of aniline, decreased its nucleophilicity, and therefore, the reactivity toward amide formation was decreased (entries 12–14 and 16 in Table I), and the presence of releasing groups, such as $-OCH_3$ or $-Oph$, increased the nucleophilicity of aniline, and therefore, the reactivity toward amide formation increased (entries 15 and 17 in Table I).

The pure benzamides were analyzed by FTIR spectroscopy. In this respect, the disappearance of two peaks at 3180–3390 cm^{-1} (NH_2) and the appearance of single peak at 3227–3350 cm^{-1} (NH) and a strong peak at 1624–1657 cm^{-1} (C=O) for primary amine, the disappearance of the single peak at 325–3400 cm^{-1} (NH), and the appearance of a strong peak at 1625–1634 cm^{-1} (C=O) for secondary amines and, finally, for the ammonia solution, the appearance of two peaks at 3180–3390 cm^{-1} (NH_2) and a strong peak at 1649 cm^{-1} (C=O) indicated the formation of the corresponding benzamides. In this method, an excess of reagent and byproducts remained bound to the resin, and the product was purified by the simple filtration and evaporation of the solvent.

In summary, we demonstrated that crosslinked poly(*N*-benzoyl-4-vinylpyridinium) chloride could act as an efficient polymeric reagent for the suspended solution phase synthesis of amides from amines. In this method, commercially available crosslinked poly(4-vinylpyridine) was used as a reagent, scavenger, and catalyst. Amides were obtained in good yields and high purity by the simple filtration and evaporation of the solvent. Exploitation of this reagent to improve the performance of other nucleophilic displacement is under investigation.

CONCLUSIONS

We believe that this procedure, which uses crosslinked poly(4-vinylpyridine), presents a useful and convenient alternative to the existing method for synthesis of amides from amines. Further application of this system in organic synthesis is currently under investigation.

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