

## A Mild, Clean, and Simple Synthesis of Symmetrical Carboxylic Anhydrides from Carboxylic Acides Using a Polymer Supported Tosyl Chloride

M.A. Karimi Zarchi\*, B.F. Mirjalili, Z. Shamsi Kahrizsangi and M. Tayefi

*Department of chemistry, Collage of Science, Yazd University, P. O. Box 89195-74, Yazd, Iran*

*(Received 18 February 2009, Accepted 27 July 2009)*

The use of polymeric reagents simplifies routine acylation of carboxylic acid because it eliminates the traditional purification. We describe the use of readily available cross-linked poly(4-vinylpyridine) supported tosyl chloride, [P<sub>4</sub>VP].TsCl, in the suspended solution phase synthesis of symmetrical anhydrides from carboxylic acids in the presence of K<sub>2</sub>CO<sub>3</sub> in high yields and purity. The products can be obtained by filtration and evaporation of the solvent.

**Keywords:** Tosyl chloride, Symmetrical anhydrides, Poly(4-vinylpyridine), Acylation

---

### INTRODUCTION

Acid anhydrides are among the most important class of reagents used in organic synthesis. They are the preferred reactive acid derivatives for the preparation of amides, esters, and peptides [1-3]. The availability of symmetrical acid anhydrides is quite essential for many transacylation applications because they do not produce any by-products due to attack at second acyl carbonyl group, which happens when mixed anhydrides are used [4]. Generally speaking, carboxylic anhydrides are prepared by carboxylic acids with powerful acylating or dehydrating agents such as acid chlorides [5], acid anhydrides [6], thionyl chlorides [4,7], DCC [8], Ketene [9], phosgene [10], chlorosulfonyl isocyanate [11] and P<sub>2</sub>O<sub>5</sub> [12]. It must be added that anhydrides have previously been prepared by the reaction of acyl halides and carboxylates [13-17], as well as by the dehydration of carboxylic acids [18-20].

However, these methods suffer from certain drawbacks that limit their applications; toxicity, high cost, low yield, instability, high reaction temperature, harsh reaction

conditions, the necessary presence of a phase-transfer catalyst and tedious work-up [21,22]. Due to the severe reaction conditions and complicated work-up to obtain anhydrides in the conventional way, it is of great significance in organic synthesis to find a simple and efficient method for the synthesis of anhydrides. Although the applications of polymeric reagent in organic synthesis have rapidly developed [23-31], reports are seldom presented for preparing Anhydrides [4,32]. Now we wish to report a very simple and efficient method for the preparation of symmetrical anhydrides from carboxylic acids.

### EXPERIMENTAL

#### Chemicals

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. The reactions were monitored by TLC, and on completion of the reaction, the pure products were obtained by simple filtrates and evaporation of the solvent. The products were characterized by comparing their IR and NMR spectra and physical data with those of authentic samples. All the yields refer to the isolated products.

---

\*Corresponding author. E-mail: makarimi@yazduni.ac.ir

### Preparation of [P<sub>4</sub>VP].TsCl

A suspension of poly(4-vinylpyridine) cross-linked with 2% DVB (1.0 g) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added to tosyl chloride (1 mmol), and it was stirred magnetically for 30 min at room temperature. The suspension was filtered and washed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 5 ml) and the cross-linked poly(4-vinylpyridine)-supported tosyl chloride (1.48 g) was obtained. The activity of this polymer was determined by potentiometric titration with a 0.1 N solution of silver nitrate. The activity of polymer was 2.0 mmol g<sup>-1</sup> of the polymer.

### General Procedure for the Preparation of Symmetrical Carboxylic Anhydrides

A suspension of cross-linked poly(4-vinylpyridine) (1.0 g) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added to tosyl chloride (1 mmol), and was stirred magnetically for 30 min at room temperature. To the resulting reaction mixture, carboxylic acid (2 mmol), and K<sub>2</sub>CO<sub>3</sub> (376 mg, 2 mmol) were added and stirring was continued for the appropriate time as indicated in Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, the suspension was filtered and washed with CH<sub>2</sub>Cl<sub>2</sub> (5 ml) and methanol (5 ml). Evaporation of the Solvent afforded the symmetrical acid anhydride in high yields (Table 1). If further purification was needed, by recrystallization from a suitable solvent provides highly pure products. The spent polymeric reagent was regenerated by treatment with sodium hydroxide solution. The regenerated polymeric reagent had the same capacity as the original form.

### Preparation of *p*-Methyl Benzoic Anhydride: A Typical Procedure

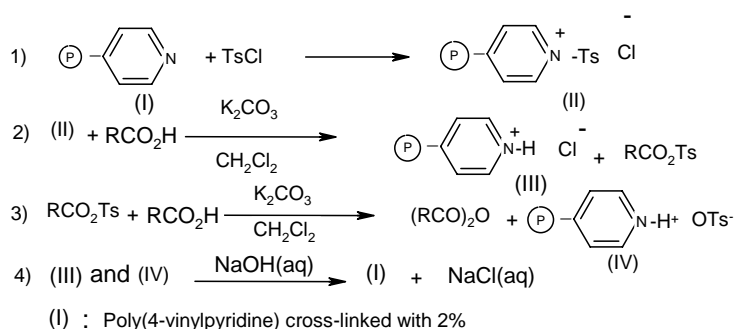
A suspension of cross-linked poly(4-vinylpyridine) (1.0 g)

in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added to tosyl chloride (1 mmol), and stirred magnetically for 30 min at room temperature. To the reaction mixture, *p*-methyl benzoic acid (304 mg, 2 mmol) and K<sub>2</sub>CO<sub>3</sub> (376 mg, 2 mmol) were added and stirred continuously for 20 min (Table 1). The progress of the reaction was monitored by TLC. After the completion of the reaction, the suspension was filtered and washed with CH<sub>2</sub>Cl<sub>2</sub> (5 ml) and methanol (5 ml). Evaporation of the solvent afforded the symmetrical *p*-methoxy benzoic acid anhydride in 96% yield (549 mg); m.p.: 93-95 °C {lit [39], 95 °C}; FTIR (KBr, cm<sup>-1</sup>): 1780, 1723 (C=O), 1608, 1575, 1447 (C=C), 1172 (C-O), <sup>1</sup>H NMR (90 MHz; CDCl<sub>3</sub>): δ (ppm) 2.38 (6 H, S, 2×CH<sub>3</sub>), 7.1-7.85 (8H, S, ArH).

## RESULTS AND DISCUSSION

Poly(4-vinylpyridine) cross-linked with 2% DVB supported tosyl chloride, [P<sub>4</sub>VP].TsCl, (II), was prepared easily by the treatment of poly(4-vinylpyridine) cross-linked with 2% DVB (I) and tosyl chloride in CH<sub>2</sub>Cl<sub>2</sub> at room temperature (Eq. 1 in Scheme 1). In this process, the mixture of cross-linked [P<sub>4</sub>VP].TsCl, carboxylic acid and K<sub>2</sub>CO<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> was stirred at room temperature as specified in Table 1.

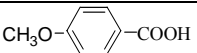
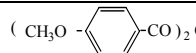
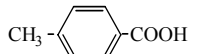
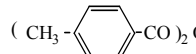
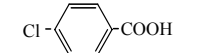

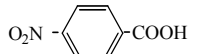
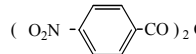
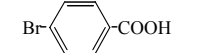
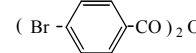
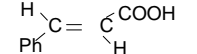
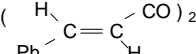
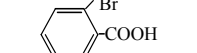
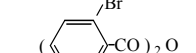
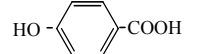
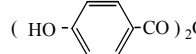
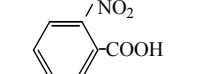
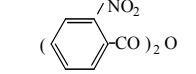
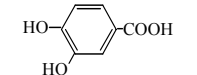
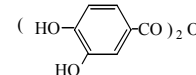
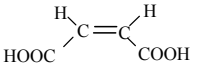
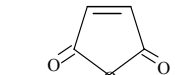
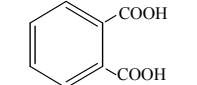
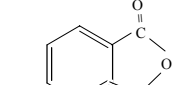
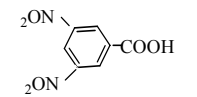
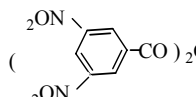
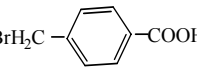
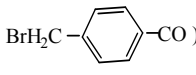
It was found that symmetrical anhydrides can be obtained in high yields from carboxylic acids in the presence of K<sub>2</sub>CO<sub>3</sub> and poly [P<sub>4</sub>VP].TsCl. By the reaction of carboxylate ions with this polymeric reagent, mixed carboxylic-sulfonic anhydrides were obtained (Eq. 2 in Scheme 1). The mixed carboxylic-sulfonic anhydrides can easily be converted to symmetrical carboxylic anhydrides by a nucleophilic acyl substitution (Eq. 3 in Scheme 1). In this process carboxylate



Scheme 1

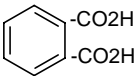
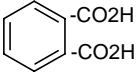
A Mild, Clean, and Simple Synthesis of Symmetrical Carboxylic Anhydrides

**Table 1.** Preparation of Symmetrical Carboxylic Anhydrides from Carboxylic Acids by [P<sub>4</sub>VP].TsCl in the Presence K<sub>2</sub>CO<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at Room Temperature

Entry	Acid	Time (min)	Product <sup>b</sup>	Yield (%) <sup>c</sup>
1		20		96
2		30		98
3		50		85
4		40		95
5		25		80
6		90		90
7		35		91
8		75		90
9		90		81
10		45		81
11		20		85
12		15		87
13		240		86
14		180		83
15	PhCOOH	120	(PhCO) <sub>2</sub> O	83

<sup>a</sup>Molar ratio of [P<sub>4</sub>VP].TsCl: carboxylic acid was 1:2 in the presence of 2 equiv. of K<sub>2</sub>CO<sub>3</sub> and the reaction performed at room temperature. <sup>b</sup>The structures were confirmed by comparison of the boiling point, melting point, IR and NMR spectra with those of authentic specimen. <sup>c</sup>Isolated yields.

**Table 2.** The Comparison of the Reaction Conditions of Different Methods of Anhydride Synthesis

Entry	Acid	Reagent	Time (min)	Temperature (°C)	Yield (%)	Ref.
1	PhCO <sub>2</sub> H	Triazine coupling	14 h	0.0	84	[40]
2	PhCO <sub>2</sub> H	[P <sub>4</sub> VP].TsCl/K <sub>2</sub> CO <sub>3</sub>	3 h	r.t	83	-
3	PhCO <sub>2</sub> H	Dabco/SOCl <sub>2</sub>	45 min	r.t	80	[35]
4	PhCO <sub>2</sub> H	P <sub>4</sub> VP/SOCl <sub>2</sub>	1 h	r.t	98.6	[4]
5	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	P <sub>4</sub> VP/SOCl <sub>2</sub>	20 min	60	100	[4]
6	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	TsCl/K <sub>2</sub> CO <sub>3</sub>	20 min	25	90	[37]
7	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Dabco/SOCl <sub>2</sub>	45 min	r.t	75	[35]
8	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	[P <sub>4</sub> VP].TsCl/K <sub>2</sub> CO <sub>3</sub>	30 min	r.t	98	-
9	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	P <sub>4</sub> VP/SOCl <sub>2</sub>	20	60	100	[4]
10	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	[P <sub>4</sub> VP].TsCl/K <sub>2</sub> CO <sub>3</sub>	20	r.t	96	-
11	4-ClC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	P <sub>4</sub> VP/SOCl <sub>2</sub>	20	60	96.6	[4]
12	4-ClC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	[P <sub>4</sub> VP].TsCl/K <sub>2</sub> CO <sub>3</sub>	50	r.t	85	-
13	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	TsCl/K <sub>2</sub> CO <sub>3</sub>	45 min	25	74	[37]
14	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Dabco/SOCl <sub>2</sub>	45 min	r.t	85	[35]
15	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	[P <sub>4</sub> VP].TsCl/K <sub>2</sub> CO <sub>3</sub>	40 min	r.t	95	-
16	PhCHCHCO <sub>2</sub> H	P <sub>4</sub> VP/SOCl <sub>2</sub>	20 min	60	89.7	[4]
17	PhCHCHCO <sub>2</sub> H	[P <sub>4</sub> VP].TsCl/K <sub>2</sub> CO <sub>3</sub>	90 min	r.t	90	-
18	2-BrC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Triazine coupling	24 h	0.0	58	[40]
19	2-BrC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	[P <sub>4</sub> VP].TsCl/K <sub>2</sub> CO <sub>3</sub>	35 min	r.t	91	-
20	2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	Dabco/SOCl <sub>2</sub>	45 min	r.t	75	[35]
21	2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	[P <sub>4</sub> VP].TsCl/K <sub>2</sub> CO <sub>3</sub>	90 min	r.t	81	-
22		Dabco/SOCl <sub>2</sub>	60 min	r.t	80	[35]
23		[P <sub>4</sub> VP].TsCl/K <sub>2</sub> CO <sub>3</sub>	15 min			

ion (the nucleophile) is replaced with tosylate ion, (a good leaving group). The hydrogen chloride produced during the reaction remains bound to poly(4-vinylpyridine) after work-up. Polymeric catalyst regeneration is easily accomplished by treatment with aqueous sodium hydroxide (Eq. 4 in Scheme 1).

This kind of mechanism has been proposed in the reaction of thionyl chloride and poly vinylpyrrolidone [33], N-methyl pyrrolidone [34], dabco [35], N,N-dimethyl formamide [36] and tosyl chloride with carboxylate ions [37]. Among the evidence that supports this mechanism is spectroscopic observation of the acyl pyridinium ion [38]. Aliphatic and

aromatic carboxylic acids were converted to the corresponding symmetrical acid anhydrides in high yields, generally > 80%. The scope and generality of this process is illustrated with several examples and the results are summarized in Table 1. The structures of all the products were identified by their melting point, spectra (IR and <sup>1</sup>H NMR) data and by direct comparison with authentic samples. This method is very fast and the work-up is very easy (only simple filtration and evaporation of the solvent). Thus, *p*-methoxy benzoic acid produces the best result with 96% yield of pure *p*-methoxy benzoic acid anhydride in 20 min (Table 1).

Dicarboxylic acid compound proceeded under the same reaction conditions to produce the expected cyclic anhydride, phthalic anhydride in 87% yield. Compared with some previously reported reagents with major or minor drawbacks, several noteworthy features of this system are apparent, including easy work-up, availability of the reagent, and simple operation. The convenient methodology of the experiment in question and its applicability to a wide variety of the cross-linked poly(4-vinylpyridine) catalyst/reagent make this method suitable for the laboratory synthesis of most symmetrical anhydrides, and the best current laboratory method for most mixed anhydrides. Our proposed method and other reported methods for the preparation of different symmetrical carboxylic anhydrides are compared as shown in Table 2.

## CONCLUSIONS

In this article we have presented poly(4-vinylpyridine).TscI reagent as a useful and convenient alternative to the existing methods for the preparation of carboxylic acid anhydrides from the salt of carboxylic acids. Further applications of this system in organic synthesis are currently under investigation.

## REFERENCES

- [1] D.S. Tarbel, *Account Chem. Res.* 2 (1969) 296.
- [2] J. Meienhofer, in: E. Gross, J. Meienhofer (Eds.), *The Peptides, Analysis, Synthesis and Biology*, Vol. 1, Academic Press, New York, 1979, Chap. 6, p. 264.
- [3] M.A. Ogliarous, J.F. Wolfe, *Synthesis of Carboxylic Acid, Esters and Their Derivatives*, Wiley, New York, 1991, pp. 198-218.
- [4] W.K. Fife, Z. Zahang, *Tetrahedron Lett.* 27 (1986) 4937.
- [5] P. Rambacher, S. Make, *Angew. Chem. Intl. Ed. Engl.* 7 (1968) 465; *Angew. Chem.* 80 (1968) 486.
- [6] S.R. Sandler, W. Karo, *Organic Functional Group Preparation*, Vol. 2, Academic Press, New York, 1972.
- [7] J.M. Adduci, R.S. Ramirez, *Org. Prep. Proced. Int.* 2 (1970) 321.
- [8] F. Chen, N.L. Benoiton, *Synthesis* (1970) 710.
- [9] Y. Kita, S. Akia, N. Ajimura, M. Yoahigi, T. Tsugoshi, H. Yasuda, Y. Tamura, *J. Org. Chem.* 51 (1986) 4150; and references cited therein.
- [10] K. Remigiusz, R. Juliatiek, M. Shahriar, *J. Org. Chem.* 59 (1994) 2913.
- [11] K.S. Keshavamurthy, Y.D. Vankar, D.N. Dhar, *Synthesis* (1982) 506.
- [12] S.G. Burton, P.T. Kaye, *Synth. Commun.* 19 (1989) 3331.
- [13] H. Adkinds, P.E. Thompson, *J. Am. Chem. Soc.* 71 (1949) 2242.
- [14] E.C. Tayo, G.W. Mclay, A. Mckillop, *J. Am. Chem. Soc.* 90 (1968) 2422.
- [15] Y. Hu, J.X. Wany, S. Li, *Synth. Commun.* 27 (1997) 243.
- [16] D. Plusquellec, F. Roulleau, M. Lefevre, E. Brown, E.C. Tayo, G.W. Mclay, A. Mckillop, *J. Am. Chem. Soc.* 90 (1968) 2422. *Tetrahedron Lett.* 44 (1988) 2471.
- [17] F. Roulleau, D. Plusquellec, E. Brown, *Tetrahedron Lett.* 24 (1983) 4195.
- [18] J.M. Wallace, J.E. Copenhaver, *J. Am. Chem. Soc.* 63 (1941) 699.
- [19] D.H. Rammer, H.G. Khorana, *J. Am. Chem. Soc.* 85 (1963) 1997.
- [20] G.P. Liesen, C.N. Sukenik, *J. Org. Chem.* 52 (1987) 455.
- [21] J. Kim, D.O. Jang, *Synth. Commun.* 31 (2001) 395.
- [22] J. Kim, Y. Park, W.S. Lee, S. Cho, Y. Yoon, *Synthesis* (2003) 1517; and references cited Therein.
- [23] a) D.C. Sherrington, P. Hodge, In *Synthesis and Separation Using Functional Polymers*, John Wiley & Sons, 1988; b) D.C. Sherrington, P. Hodge, In *Polymer-*

- Supported Reactions in organic Synthesis, John Wiley & Sons, 1980; c) K. Tkemoto, Y. Inaki, R.M. Ottenbrite, In *Functional Monomers and Polymers*, Marcel Dekker Inc., New York, 1987.
- [24] a) A. Akelah, D.C. Sherington, *Chem. Rev.* 8 (1981) 577; b) A. Akelah, D.C. Sherington, *Polymer* 2 (1984) 1369.
- [25] S.V. Ley, I.R. Baxendale, R.N. Bream, P.S. Jackson, A.G. Leach, D.A. Longbottom, M. Nesi, J.S. Scott, R.I. Storer, S.J. Taylor, *J. Chem. Soc. Perkin Trans 1* (2000) 3815.
- [26] B. Tamami, N. Iranpoor, M.A. Karimi Zarchi, *Polymer* 34 (1993) 2011.
- [27] B. Tamami. M.A. Karimi Zarchi, *Eur. Polym. J.* 31 (1995) 715.
- [28] M.A. Karimi Zarchi, A. Zarei, *J. Chin. Chem. Soc.* 52 (2005) 309.
- [29] M.A. Karimi Zarchi, J. Noei, *J. Appl. Polym. Sci.* 104 (2007) 1064.
- [30] M.A. Karimi Zarchi, *J. Chin. Chem. Soc.* 54 (2007) 1299.
- [31] M.A. Karimi Zarchi, B.B.F. Mirjalili, N. Ebrahimi, *Bull. Korean. Chem Soc.* 29 (2008) 1079.
- [32] J.G. Rodrigues, R.M. Villamil, S. Ramos, *New J. Chem.* (1998) 865.
- [33] B. Tamami, A.R. Kiasat, *J. Chem. Res.* (1999) 444.
- [34] F. Hiashi, J. Nishi, *J. Polym. Sci. A* (1986) 701.
- [35] F. Kazemi, A.R. Kiasat, *Phosphorous, Sulfur and Silicon* 178 (2003) 2287.
- [36] M.S. Newman, P.K. Sujeeth, *J. Org. Chem.* (1978) 4367.
- [37] F. Kazemi, H. Sharghi, M.A. Naseri, *Synthesis* (2004) 205.
- [38] R.A. Fersht, W.P. Jencks, *J. Am. Chem. Soc.* 92 (1970) 5432.
- [39] J. Buckingham, S.M. Donaghy. *Dictionary of Organic Compounds*, 5<sup>th</sup> ed., Chapman and Hall, New York, 1982.
- [40] Z.J. Kaminski, B. Kolesinska, M. Malgorzata. *Synthetic Commun.* 34 (2004) 3349