p-Toluenesulfonyl Chloride (p-TsCl) as a New and Effective Catalyst for Acetylation and Formylation of Hydroxyl Compounds under Mild Conditions

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Abstract

The first catalytic application of p-TsCl for efficient acetylation of various types of alcohols and phenols with acetic anhydride in both solution and solvent-free conditions is reported. Also structurally diverse alcohols were formylated using formic acid based on the use of catalytic amount of p-TsCl under solvent-free condition. The reactions were carried out in short reaction time and in good to excellent yields at room temperature.

Key words: p-Toluenesulfonyl Chloride, Hydroxyl compounds, Acetylation , Formylation

Introduction

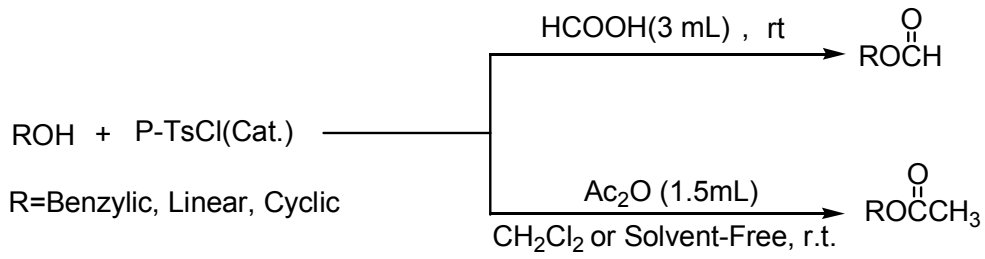
The protection of hydroxyl group is often necessary during the course of various transformations in a synthesis sequence, in particular in the construction of polyfunctional molecules such as nucleosides, carbohydrates, steroids, and natural products [1]. Among the various protecting groups used for the hydroxyl function, acetyl is the most common group because of the ease of formation as well as mild conditions for deprotection [1,2]. In addition, the ester moiety is a common functional group in polymers, drugs, and biologically relevant compounds. The most commonly used reagent combination for this reaction is acid anhydride in the presence of acid or base catalysts [3,16]. Formylation is also a very important process because the formate esters serve as a useful synthetic reagent and intermediate. In addition, deformylation can be affected selectively in the presence of acetate or other ester protecting group [1], furthermore if the alcoholic group is planned to be oxidized later in

synthetic scheme, the formylated alcoholic group need not be deprotected and direct oxidation can be realized [17].

Due to the instability of the anhydride and the acid chloride of formic acid, formylation of alcohols by formic acid and transesterfication using ethyl formate are important synthetic reactions. Several catalysts, such as $Sc(OTf)_3$ [18], TMSOTf [19] , PPh_3/CBr_4 [20], $In(OTf)_3$ [21], Bi(OTf)3 [22], $KCoW_{12}O_{40}.3H_2O$ [23], Chloral [24], $Al(HSO_4)_3$ [25], $(NH_4)_8[CeW_{10}O_{36}]. H_2O$ [26], Silphos [27] and Silica Triflate [28] have been used for fomylation with formic acid.

RESULT AND DISCUSSION

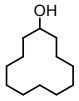
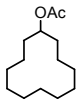
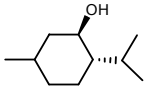
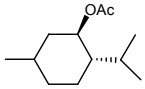
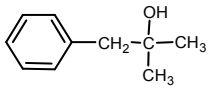
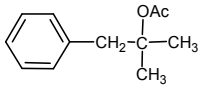
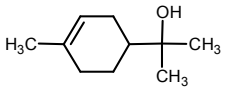
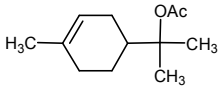
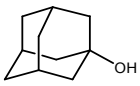
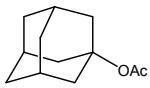
In continuation of our studies on catalytic application of *N*-halo compounds as organocatalysis in organic chemistry [30,34] , We have found that *p*-toluenesulfonyl chloride,, as an inexpensive commercially available used widely as sulfonyl transfer reagent [35], has found little application use as chlorinating agent [36]. Also, to the best of our knowledge, there is no report on catalytic application of *p*-toluenesulfonyl chloride as S-halo reagent in organic transformations. In this present research, we wish to report the catalytic application of *p*-toluenesulfonyl chloride as a source of "Cl+" for the efficient acetylation and formylation of a wide range of hydroxyl compounds under mild conditions (Scheme 1).



Scheme 1

We first investigated the acetylation of variety of alcohols using Ac_2O in the presence of catalytic amount of *p*-TsCl in CH_2Cl_2, at room temperature. The results were summarized in Table 1.

Table 1. **Acetylation of the alcohols using Ac_2O catalyzed with *p*-TsCl in CH_2Cl_2 at room temperature**

Entry	Substrate	ROH/TsCl/Ac_2O	Time (h)	Product[a]	Yields (Isolated) (%)
1	4-Cl-$C_6H_4CH_2OH$	1/0.05/2	6	4-Cl-$C_6H_4CH_2OAc$	۴۹
2	2,4-$(Cl)_2C_6H_3CH_2OH$	1/0.01/4	5.32	2,4-$(Cl)C_6H_3CH_2OAc$	۰۹
3	$PhCH_2CH_2OH$	1/0.01/4	6.5	$PhCH_2CH_2OAc$	95
4	phCH(OH)Ph	1/0.01/4	9		89
5	$PhCH(OH)CH_3$	1/0.01/4	4.15	$PhCH(OAc)CH_3$	85
6		1/0.01/4	7.32		87
7		1/0.01/4	7		۸0
8		1/0.1/4	7.12		93
9		1/0.1/4	23		82
10		1/0.1/10	28		83

[a]All products were characterized by comparison of their spectral data (^{1}H-NMR; IR) with those of authentic samples.

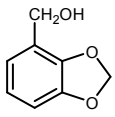
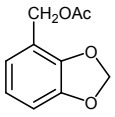
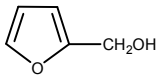
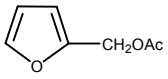
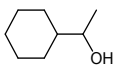
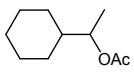
Also, we have found that *p*-TsCl can be catalyzed acetylation of alcohols under solvent-free conditions in very shorter reaction time than solution conditions.

In order to optimize the reaction conditions we first examined acetylation reactions of 1.0 mmol of 4-Chlorobenzyl alcohol with different amounts of *p*-TsCl (0.05-0.15 mmol) and

Ac_2O (1-2 mL) at room temperature under solvent-free conditions. It was observed that 0.1 mmol of *p*-TsCl in 1.5 mL Ac_2O gave the best results and produced acetate in very short reaction time and in quantitative yields. In order to extend the scope of this acetylation reaction, the variety of hydroxyl compounds including primary, secondary, tertiary, benzylic alcohols, diols and phenols were subjected (Table 2) for this catalyst.

As shown in Table 2, in the case of primary and secondary alcohols the reactions were completed very rapidly. Interestingly, different types of highly hindered tertiary alcohols were successfully converted to the corresponding acetate in almost quantitative yields under solvent-free conditions at room temperature. In this reaction conditions, there were no elimination products in the mixture. This method tolerates other functionalities on the substrate such as double bonds (Table 2). Also, the data in Table 2 clearly show that diols and phenols were successfully converted to the corresponding acetate quantitative yields within a short reaction time (Table 2).

Table 2. **Acetylation of the alcohols or phenols (1 mmol) using Ac_2O (1.5 mL) catalyzed with *p*-TsCl (0.1 mmol) under solvent-free conditions at room temperature**

Entry	Substrate	Time (min)	Product[a]	Yields (Isolated) (%)
1	4-OMe-$C_6H_4CH_2OH$	9	4-OMe-$C_6H_4CH_2OAc$	۷۸
2	4-Cl-$C_6H_4CH_2OH$	7	4-Cl-$C_6H_4CH_2OAc$	۰۹
3	2,4-$(Cl)_2C_6H_3CH_2OH$	15	2,4-$(Cl)C_6H_3CH_2OAc$	۰۹
4	4-F-$C_6H_4CH_2OH$	8	4-F-$C_6H_4CH_2OAc$	83
۶		30		89
		18		85
7	$PhCH_2CH_2OH$	30	$PhCH_2CH_2OAc$	85
8	$PhCH=CHCH_2OH$	20	$PhCH=CHCH_2OAc$	95
9	$CH_3(CH_2)_4CH(OH)CH_3$	25	$CH_3(CH_2)_4CH(OAc)CH_3$	93
		43		۹۵

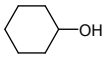
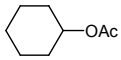
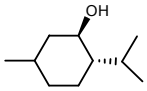
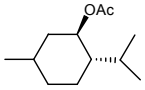
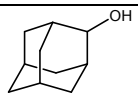
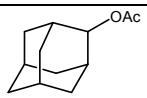
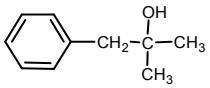
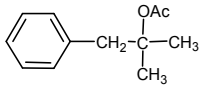
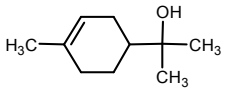
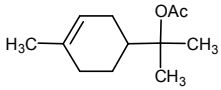
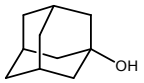
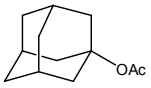
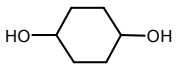
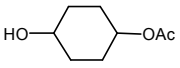
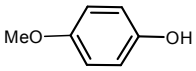
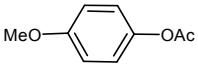
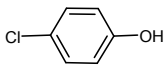
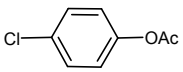
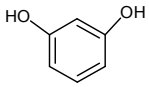
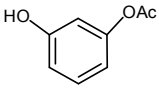
11		33		96
12		83		۸9

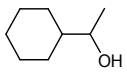
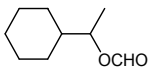
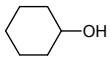
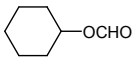
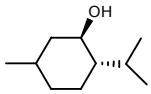
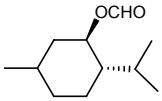
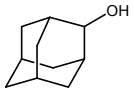
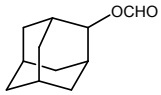
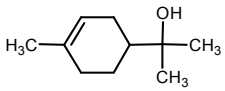
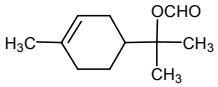
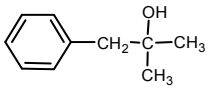
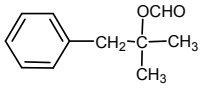
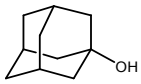
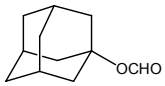
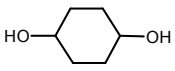
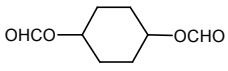
Table 2. **Continued**

Entry	Substrate	Time (min)	Product	Yields[a](Isolated) (%)
13		30		86
14		180		81
15		115		75
16		25h		87
17		23		88[b]
18		3		95
19		67		79
20		80		86

[a]All products were characterized by comparison of their spectral data ([1]H-NMR; IR) with those of authentic samples. [b]The ratio ROH/*p*-TsCl/Ac2O is 1/0.2/3 mL

Subsequently, we discovered that formylation of a diverse range of alcohols can be carried out to obtain the corresponding formate with formic acid in the presence of the same catalyst in good to excellent yields within a short reaction time under solvent-free conditions at room temperature (Scheme 1 and Table 3).

Table 3. **Formylation of alcohols using acid formic (3 mL) in the presence of catalytic amount of *p*- TsCl (0.15 mmol) at room temperature**

Entry	Substrate	Time (min)	Product[a]	Yields (Isolated) (%)
1	4-Cl-$C_6H_4CH_2OH$	10	4-Cl-$C_6H_4CH_2OCHO$	88
2	4-F-$C_6H_4CH_2OH$	5	4-F-$C_6H_4CH_2OCHO$	96
3	4-NO_2-$C_6H_4CH_2OH$	54	4-NO_2-$C_6H_4CH_2OCHO$	85
4	2,4-$(Cl)_2C_6H_3CH_2OH$	10	2,4-$(Cl)C_6H_3CH_2OCH$	90
5	$PhCH_2CH_2OH$	8	$PhCH_2CH_2OCHO$	92
6	PhCH(OH)Ph	4	PhCH(OCHO)Ph	89
7	$CH_3CH(Ph)OH$	6	$CH_3CH(Ph)OCHO$	82
8		10		91
9		9		79
10		10		84
11		20		92
12		55		90
13		48		56
14		15h		77
15		38		93[b]

[a]All products were characterized by comparison of their spectral data (^{1}H-NMR; IR) with those of authentic Samples. [b]The ratio ROH/*p*-TsCl/HCOOH is 1/0.3/6 mL

The actual role of *p*-TsCl is not clear. However on the basis of previously reported mechanism for applying of *p*-TsCl for α-chlorination of ketones [36], one explanation is that *p*-TsCl might act as a source for the formation of Cl^+ which in turn activates the carbonyl group of Ac_2O (as a Lewis acid).

However, at this time the precise role of *p*-TsCl is not clear and the actual role of this reagent should be further studied in detail.

CONCLUSIONS

In conclusion we have report the first example for catalytic application of *p*-TsCl as an inexpensive and commercial available catalyst for acetylation and formylation of hydroxyl groups. The selectivity, easy and clean work up, short reaction times and good to high yields are the main advantages of our protocol.

EXPERIMENTAL SECTION

General Procedure for Acetylation of Alcohols and Phenols Using Ac_2O Catalyzed with *p*-TsCl in CH_2Cl_2:

Alcohols (1 mmol) were added to a mixture of Ac_2O (2-4 mmol) and *p*-TsCl (0.05- 0.1 mmol) in CH_2Cl_2 (5 mL), and then the mixture was stirred at room temperature for the specified time (Table 1). The progress was monitored by TLC. After completion of the reaction, 10 % aqueous NaOH (10 mL) was added, then the esters were extracted with CH_2Cl_2 (3×10 mL) and the organic layer was dried over anhydrous Na_2SO_4. Evaporation of the CH_2Cl_2 under reduced pressure gave almost pure products. In some case, flash column chromatography on silica gel (hexane/EtOAc 10:1) provided pure.

General Procedure for Acetylation of Alcohols and Phenols Using Ac_2O Catalyzed with *p*-TsCl under Solvent-Free Conditions:

To a mixture of Ac_2O (1.5 mL) and *p*-TsCl (0.1 mmol), alcohols or phenols (1 mmol) were added, and then the mixture was stirred at room temperature for the specified time (Table 2). The progress was monitored by TLC. After completion of the reaction, 10% aqueous NaOH (5 mL) was added, then the esters were extracted with CH_2Cl_2 (3×10 mL) and the organic layer was dried over anhydrous Na_2SO_4. Evaporation of the CH_2Cl_2 under reduced

pressure gave almost pure products. In some case, flash column chromatography on silica gel (hexane/EtOAc 10:1) provided pure.

General Procedure for Formylation of Alcohols Catalyzed with *p*-TsCl under Solvent-Free Conditions:

The alcohol (1 mmol) was added to a mixture of HCOOH (3 mL) and *p*-TsCl (0.15 mmol). The mixture was stirred vigorously at room temperature for the specified time (Table 3). After completion of the reaction (TLC), 10% aqueous NaOH (10 mL) was added, the mixture was stirred for additional 5 min. Then the ester was extracted with CH_2Cl_2 (3×10 mL) and the organic layer was dried over anhydrous Na_2SO_4. Evaporation of the CH_2Cl_2 under reduced pressure gave almost pure products. In some case, flash column chromatography on silica gel (hexane/EtOAc 10:1) provided pure.

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References

1- Kocienski, P. J. Protecting Groups, Thieme: Stuttgart, 1994.

2- Greene, T.W. Wuts, P.G.M. Protective Groups in Organic Synthesis, third ed., Wiley, NY, 1999.

3- Izumi, J. Shiina, I. Mukaiyama, T. Chem. Lett., 24 1995, 141.

4- K.; Ishihara, M.; Kubota, H. Yamamoto, Synlett. 1996, 265.

5- P.A.; Procopiou, S. P. D.; Baugh, S. S.; Flack, G. G. A. Ingles, J. Org. Chem. 63, 1998,2342.

6- S. P.; Chavan, R.; Anand, K.; Pasupathy, B.S. Rao, Green Chem. 3, 2001, 320.

7- S.; Paul, P.; Nanda, R.; Gupta, A. Loupy, Tetrahedron Lett., 432002, 4261.

8- S. G.; Lee, J. H. Park, J. Mol. Catal. A: Chem. 194, 2003,49.

9- R.; Ghosh, M.; Swarupananda, A. J. Chakraborty, Tetrahedron Lett. 45, 2004, 6775.

10- R.; Ghosh, M.; Swarupananda, A. Chakraborty, Tetrahedron Lett., 46, 2005147.

11- N.; Ahmed, J. E. V. Lier, Tetrahedron Lett. 47, 2006,5345.

12- K.; Jeyakumar, D.K. Chand, J. Mol. Catal. A: Chem. 2006, 255, 275.

13- M. M.; Heravi, F. K.; Behbahani, R. H.; Shoar, H. A. Oskooie, Catal. Commun. 7, 2006, 136.

14- J. W. J.; Bosco, A.; Agrahari, A. K. Saikia, Tetrahedron Lett. 472006,, 4065.

15- T. S.; Reddy, M.; Narasimhulu, N.; Suryakiran, K.C.; Mahesh, K.; Ashalatha, Y. Venkateswarlu, Tetrahedron Lett. 47, 2006, 6825.

16- B.; Das, P. Thirupathi,. J. Mol. Catal. A: Chem. 269, 2007, 12.

17- B,; Elali, H. Alper, 96, 1995,197.

18- K.; Ishihara, M.; Kubota, H.; Kurihara, H. Yamamoto, J. Am. Chem. Soc. 1171995,, 4413.

19- P. A.; Procopiou, S. P. D.; Baugh, S.S.; Flack, G.A. Inglis, Chem. Commun. 1996, 2625.

20- H.; Hagiwara, K.; Morohashi, H.; Sakai, M. Ando, Tetrahedron. 54, 1998, 5845.

21- K. K.; Chauhan, C. G.; Frost, I.; Love, D. Waite, Synlett. 1999, 1743.

22- A.; Orita, C.; Tanahashi, A.; Kakuda, J. Otera, Angew. Chem. Int. Ed. 39, 2000, 2877.

23- M. H.; Habibi, S.; Tangestaninejad, V.; Mirkhani, B. Yadollahi, Tetrahedron. 57, 2001, 8333.

24- R. N.; Ram, N. K. Meher, Tetrahedron. 58, 2002,2997.

25- F.; Shirini, M. A.; Zolfigol, M.; Abedini, P Salehi, Bull. Korean Chem. Soc. 24, 2003,1683.

26- V.; Mirkhani, S.; Tangestaninejad, M.; Moghadam, B.; Yadollahi, L. Alipanah, fur Chemie. 135,2004, 1257.

27- N.; Iranpoor, H.; Firouzabadi, A. Jamalian, Silphos Tetrahedron Lett. 46, 2005,7963.

28- F.; Shirini, K.; Marjani, H.; Taherpour-Nahzomi, M. A. Zolfigol, Phosphorus, Sulfur, and Silicon. 182, 2007,1245.

29- P. I.; Dalko, L. Moissan, Angew. Chem. Int. Ed., 43, 20045138 (b) Duthaler, R. O. Angew. Chem. Int. Ed. 2003, 42, 975.

30- A.; Khazaei, A.; Rostami, Z.; Tanbakouchian, Z. Zinati, Catal. Commun. 7, 2006, 214.

31- A.; Khazaei, A.; Rostami, M. Mahboubifar, Catal. Commun. 8, 2007,383.

32- A.; Khazaei, A.; Rostami, S.; Rahmati, M. Mahboubifar, Phosphorus, Sulfur., 182, 2007537.

33- A.; Khazaei, M. A.; Zolfigol, A.; Rostami, A. Ghorbani-Choghamarani, Catal. Commun. 8, 2007, 543.

34- A.; Khazaei, A.; Rostami, Z.; Tanbakouchian, Z. Zinati, J. Braz. Chem. Soc. 17, 2006, 206.

35- A.; Khalafi-Nezhad, A.; Parhami, M. V.; Soltani-Rad, A. Zarea, Tetrahedron Lett. 46, 2005, 6879, and references therein.

36- K. M.; Brummond, K. D. Gesenberg, Tetrahedron Lett. 1999, 40, 2231.