EFFICIENT AND CONVENIENT SYNTHESIS OF SYMMETRICAL CARBOXYLIC ANHYDRIDES FROM CARBOXYLIC ACIDS WITH SULFATED ZIRCONIA BY PHASE TRANSFER CATALYSIS

Yu Lin Hu[1], Xing E Zhao[2] and Ming Lu[1*]

[1]Chemical Engineering College, Nanjing University of Science and Technology, Nanjing 210094, PR China
[2]Nanjing Simcere Pharmaceutical Co., Ltd, Nanjing 210042, PR China

ABSTRACT. An efficient and convenient procedure for the synthesis of symmetrical carboxylic anhydrides from carboxylic acids with sulfated zirconia by PEG-1000 phase transfer catalysis has been developed. The reactions proceeded under mild and solvent-free conditions to provide the carboxylic anhydrides in good to excellent yields. The product can be isolated by a simple extraction with organic solvent, and the catalyst system can be recycled or reused without any significant loss of catalytic activity.

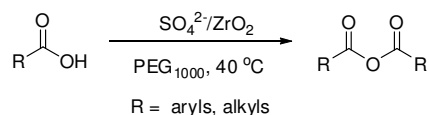**KEY WORDS**: Carboxylic anhydrides, Carboxylic acids, SO_4^{2-}/ZrO_2, Phase transfer catalysis

INTRODUCTION

Carboxylic anhydrides are important classes of chemicals that have been used extensively as synthetic intermediates in the preparation of a variety of fine or special chemicals such as amides, esters, peptides, drugs, etc [1-3], and many publications in the open literature have been found in synthesis of these type of compounds [3]. Generally speaking, they are prepared by dehydration of carboxylic acids with powerful acylating or dehydrating agents such as acid chlorides [4], acid anhydrides [5], thionyl chlorides [6, 7], sulfonyl chlorides [8], phophoranes [9], phosgene [10], pyridazin-3(2H)-ones [11, 12], ketene [13], imidazolinium chlorides [14], 1,3,5-triazines [15], DCC [16], dinitrogen tetroxide [17], chlorosulfonyl isocyanate [18], carbodiimides [19], trichloroacetonitrile/triphenylphosphine [20], and P_2O_5 [21]. Carboxylic anhydrides can also be prepared by the reaction of acid chlorides with carboxylates [22, 23] or carboxylic acids [24-27], as well as by reaction of acid chlorides under ultrasound basic media [28]. However, some of these procedures are invariably associated with one or more disadvantages such as long reaction time, high temperature, low yields and harmful to the environment. Consequently, there is a great need to develop new and environment-benign procedures that address these drawbacks for the synthesis of anhydrides.

Phase transfer catalysis (PTC) is a versatile synthetic technique that has been widely applied to intensify otherwise slow heterogeneous reactions involving an organic substrate and an ionic reactant, either dissolved in water (liquid-liquid) or present in solid state (liquid-solid) [29, 30]. In addition, phase transfer catalysis can make reaction condition gentle, can effectively avoid side reaction to occur, can reduce consumption of organic solvent and raw materials and enhance the efficiency of organic synthesis. At present, phase transfer catalysis has been applied in various organic syntheses, such as electrophilic substitution reaction, nucleophilic substitution reaction, hydrolysis and so on [31-34]. Recently, the use of zirconia based solid acids has been received considerable attention in different areas of organic synthesis, because of their environmental compatibility, reusability, greater selectivity, operational simplicity, nontoxicity, noncorrosiveness, low cost and ease of isolation [35]. Among the promoted ZrO_2 solid acid catalysts, the sulfated zirconia (SO_4^{2-}/ZrO_2) become more popular because of its

_____
*Corresponding author. E-mail: luming1963@163.com

strong acidity and high activity in light alkane conversions at relatively mild temperatures [36, 37]. In this paper, we wish to report an efficient and convenient method for the preparation of symmetrical carboxylic anhydrides from the corresponding carboxylic acids with sulfated zirconia by phase transfer catalysis without any organic solvents (Scheme 1).

Scheme 1. Synthesis of symmetrical carboxylic anhydrides.

EXPERIMENTAL

Apparatus and reagents

All the chemicals used were from commercial sources without any pretreatment. All the reagents were of analytical grade. ^{1}H NMR spectra were recorded on a Bruker 400-MHz spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard. Elemental analyses were performed on a Vario EL III instrument (Elmentar Anlalysensy Teme GmbH, Germany). High performance liquid chromatography (HPLC) experiments were performed on a liquid chromatograph (Dionex Softron GmbH, USA), consisting of a pump (P680) and ultraviolet-visible light detector (UVD) system (170U). The experiments were performed on Diacovery C18 column, ø 4.6 × 250 mm. IR spectra were recorded on a Perkin Elmer PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}.

Preparation of sulfated zirconia

The sulfated zirconia catalyst was prepared by equilibrium adsorption of sulfate species on the surface of hydrous zirconium oxide samples. The hydrous zirconia catalysts were prepared by precipitation method using $ZrOCl_2 \cdot 8H_2O$ and liquid ammonia solutions. Required amount of zirconyl chloride solution was added dropwise to deionised water. The pH was maintained at 10.0 by controlled addition of ammonia solution to the reaction mixture. The precipitated solution was stirred for 16 h at 35 °C followed by filtration and washing with double distilled water until free from chlorine ions. The hydroxide precipitate were subsequently dried overnight at 100 °C and calcined at 250 °C for 24 h. To prepare sulfated ZrO_2 catalyst, a portion of the obtained hydrous zirconia sample was ground to fine powder and immersed in 1 M H_2SO_4 solution. Excess water was evaporated on a water-bath and the resulting sample was oven-dried at 120 °C for 12 h and calcined at 500 °C for 4 h in air atmosphere and stored in vacuum desiccator.

General procedure for the preparation of symmetrical carboxylic anhydrides

To a stirred solution of carboxylic acid (10 mmol) and PEG-1000 (5 mmol) was added SO_4^{2-}/ZrO_2 (3 mmol) at room temperature and stirring was continued at 40 °C for the appropriate time. After completion of the reaction, as indicated by HPLC, the product was extracted with methylene chloride (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then filtered over a pad of flash silica gel. Removal of the solvents in vacuo furnished the corresponding pure symmetrical carboxylic anhydrides. Fresh substrates were then recharged to the recovered catalyst system and then recycled under identical reaction

conditions. The target substrates were characterized by elemental analysis, ^{1}H NMR or compared with their authentic samples. Spectroscopic data for selected products are given below.

4-Methylbenzoic anhydride (Table 2, entry 1). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 2.28 (s, CH$_3$, 3H), 7.32 (m, Ar-H, 2H), 7.86 (m, Ar-H, 2H). Anal. calcd for C$_{16}$H$_{14}$O$_3$: C, 75.54; H, 5.55; O, 18.89. Found: C, 75.57; H, 5.55; O, 18.88. IR (KBr, cm^{-1}): 2917, 2830, 1782, 1734, 1641, 1608, 1514, 1432, 1383.

4-Methoxybenzoic anhydride (Table 2, entry 2). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 3.72 (s, CH$_3$, 3H), 7.27 (m, Ar-H, 2H), 7.89 (m, Ar-H, 2H). Anal. calcd for C$_{16}$H$_{14}$O$_5$: C, 67.11; H, 4.92; O, 27.95. Found: C, 67.13; H, 4.93; O, 27.94. IR (KBr, cm^{-1}): 2949, 2825, 1785, 1730, 1637, 1612, 1522, 1381, 1258.

4-Nitrobenzoic anhydride (Table 2, entry 4). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 8.19 (m, Ar-H, 2H), 8.37 (m, Ar-H, 2H). Anal. calcd for C$_{14}$H$_8$N$_2$O$_7$: C, 53.12; H, 2.55; N, 8.87; O, 35.44. Found: C, 53.17; H, 2.55; N, 8.86; O, 35.42. IR (KBr, cm^{-1}): 1789, 1741, 1634, 1620, 1517, 1508, 1353.

Glutaric anhydride (Table 2, entry 10). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 1.97 (m, CH$_2$, 2H), 2.26 (t, 2×CH$_2$, 4H). Anal. calcd for C$_5$H$_6$O$_3$: C, 52.61; H, 5.28; O, 42.09. Found: C, 52.63; H, 5.30; O, 42.07. IR (KBr, cm^{-1}): 2967, 2861, 1781, 1730, 1635, 1609, 1519, 1457.

Succinic anhydride (Table 2, entry 11). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 2.94 (s, CH$_2$, 2H). Anal. calcd for C$_4$H$_4$O$_3$: C, 48.01; H, 4.03; O, 47.96. Found: C, 48.01; H, 4.03; O, 47.96. IR (KBr, cm^{-1}): 2963, 2867, 1788, 1732, 1629, 1611, 1516, 1462.

2-Phenylacetic anhydride (Table 2, entry 17). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 3.64 (s, CH$_2$, 2H), 7.27-7.38 (m, Ar-H, 5H). Anal. calcd for C$_{16}$H$_{14}$O$_3$: C, 75.55; H, 5.53; O, 18.87. Found: C, 75.57; H, 5.55; O, 18.88. IR (KBr, cm^{-1}): 2957, 2863, 1786, 1739, 1630, 1614, 1519, 1467.

RESULTS AND DISCUSSION

The initial study was carried out using benzoic acid as the substrate to optimize the reaction conditions, and the results are summarized in Table 1. At first, eight type of phase transfer catalysts, PEG-200, PEG-400, PEG-600, PEG-800, PEG-1000, cetyltrimethylammonium bromide (CTAB), etradecyltrimethylammonium bromide (TTAB), and tetraethylammonium bromide (TEAB), were tested with SO$_4^{2-}$/ZrO$_2$ as the catalyst precursor in the reaction (Table 1, entries 1-8), it was observed that PEG-1000 demonstrated the best performance, providing a 95% high yield (Table 1, entry 5). In addition, the catalyst SO$_4^{2-}$/ZrO$_2$ and PEG-1000 are crucial for this reaction, and the lack of any component leads to no reaction or a lower yield. (Table 1, entries 9 and 10). Therefore, the combination of SO$_4^{2-}$/ZrO$_2$ and PEG-1000 was chosen as the optimal catalyst system for further exploration.

The influences of the amount of the catalyst SO$_4^{2-}$/ZrO$_2$ on the reaction at 40 °C are shown in Figure 1. No reaction occurred in the absence of the catalyst, the increase of the catalyst amount (i.e. the ratio of (SO$_4^{2-}$/ZrO$_2$)/benzoic acid increased) enhanced the reaction and the yield reached maximum at 0.3 of the ratio. However, further addition of the catalyst resulted in the slow decrease of the yield.

Figure 2 shows the influences of reaction temperature on the reaction. The catalytic activity increased with the increase in reaction temperature, and the yield reached maximum at 40 °C. However, further increase in the temperature, decreased slowly the yield. These results show that the moderate temperature, such as 40 °C enhanced the reaction.

Table 1. Optimization of the reaction conditions for the synthesis of benzoic anhydride from benzoic acid[a].

Entry	Phase transfer catalyst	Catalyst	Time (h)	Yield (%)[b]
1	PEG-200	SO_4^{2-}/ZrO_2	2	85
2	PEG-400	SO_4^{2-}/ZrO_2	2	87
3	PEG-600	SO_4^{2-}/ZrO_2	1	91
4	PEG-800	SO_4^{2-}/ZrO_2	1	94
5	PEG-1000	SO_4^{2-}/ZrO_2	1	95
6	CTAB	SO_4^{2-}/ZrO_2	1	93
7	TTAB	SO_4^{2-}/ZrO_2	2	87
8	TEAB	SO_4^{2-}/ZrO_2	2	84
9	—	SO_4^{2-}/ZrO_2	6	81
10	PEG-1000	—	12	0

[a]Reaction conditions: benzoic acid (10 mmol), SO_4^{2-}/ZrO_2 (3 mmol), PTC (5 mmol), 40 °C. [b]Isolated yield.
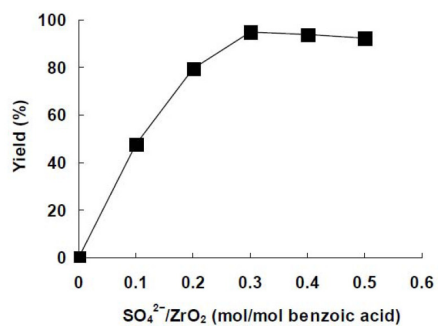
Figure 1. Influences of amount of SO_4^{2-}/ZrO_2 on the reaction.
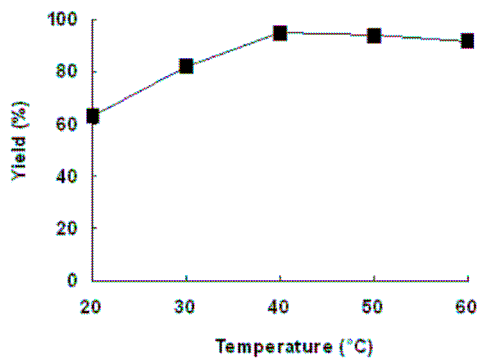
Figure 2. Influences of temperature on the reaction.

In addition, the catalyst system could be typically recovered and reused for subsequent reactions (Figure 3). The recycling process involved the product layer (upper layer) was extracted with methylene chloride and the catalyst system layer (under layer) was concentrated to remove water produced in the reaction under vacuum. Fresh substrates were then recharged to the recovered catalytic system and the mixture was heated to react once again, and only 2.5% loss of weight was observed after 6 times recycling.
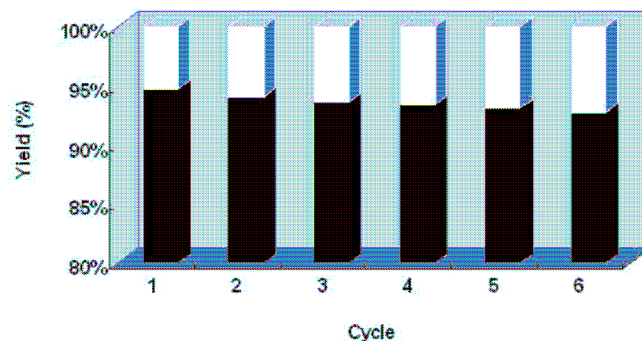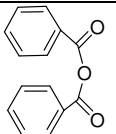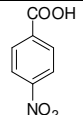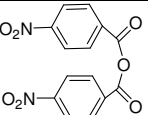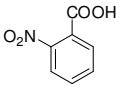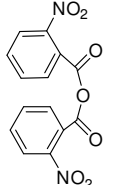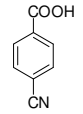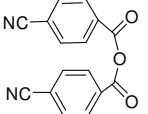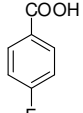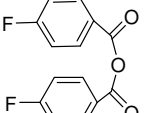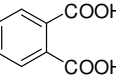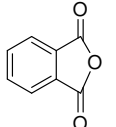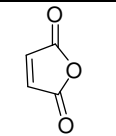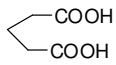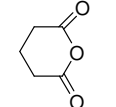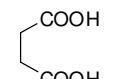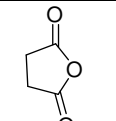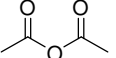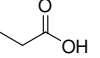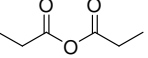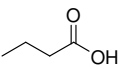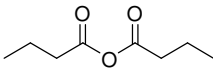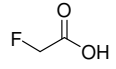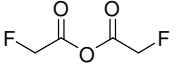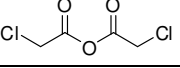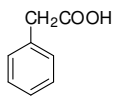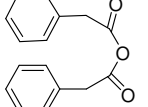
Figure 3. Repeating reactions using recovered catalyst system.

With these results in hand, the catalyst system was then applied to various carboxylic acids as summarized in Table 2. It is clear that various types of aromatic and alkyl acids, both monoacidic and dibasic, have been successfully converted to the corresponding carboxylic anhydrides in good to high yields (Table 2, entries 1-17), whereas the alkyl acids were less reactive, and the reactions proceeded more slowly, and longer reaction time was needed to reach good yields (Table 2, entries 9-17). Surprisingly, the conversion of dicarboxylic acids to the corresponding carboxylic anhydrides is faster and more efficient than that of monocarboxylic acids (Table 2, entries 8-11). In addition, the electron deficiency and nature of the substituents have influence on the conversion rate, carboxylic acids having electron-withdrawing groups (Table 2, entries 4-7 and 15-17) react more faster than those having electron-donating groups (Table 2, entries 1 and 2, 13 and 14).

Table 2. SO_4^{2-}/ZrO_2/PEG-1000-mediated conversion of carboxylic acids into carboxylic anhydrides[a].

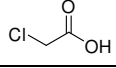| Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	COOH / CH_3	H_3C— / H_3C—	1.5	94
2	COOH / OCH_3	H_3CO— / H_3CO—	1.5	93

3	COOH (benzoic acid)	benzoic anhydride	1	95
4	COOH, NO_2 (4-nitrobenzoic acid)	bis(4-nitrobenzoic) anhydride, O_2N	0.5	97
5	O_2N, COOH (2-nitrobenzoic acid)	NO_2 anhydride	0.5	96
6	COOH, CN (4-cyanobenzoic acid)	NC anhydride	0.5	95
7	COOH, F (4-fluorobenzoic acid)	F anhydride	0.5	93
8	COOH, COOH (phthalic acid)	phthalic anhydride	0.5	98
9	COOH, COOH (maleic acid)	maleic anhydride	1	96
10	COOH, COOH (glutaric acid)	glutaric anhydride	1.5	95
11	COOH, COOH (succinic acid)	succinic anhydride	1.5	94
12	O, OH (acetic acid)	acetic anhydride	2	90
13	O, OH (propionic acid)	propionic anhydride	2.5	88

14			3	85
15			1.5	92
16			1.5	91
17	CH₂COOH		1.5	93

[a]Reaction conditions: carboxylic acid (10 mmol), SO_4^{2-}/ZrO_2 (3 mmol), PEG-1000 (5 mmol), 40 °C. [b]Isolated yield.

CONCLUSIONS

In conclusion, we have disclosed an easy and straightforward high yielding preparation of various symmetrical carboxylic anhydrides by reaction of carboxylic acids with sulfated zirconia by PEG-1000 phase transfer catalysis. Most importantly, the catalysts are very easy to handle and can be recycled and reused without any significant loss of catalytic activity. The definition of the mechanism and the extension of this method to the synthesis of unsymmetrical carboxylic anhydrides are currently under investigation.

ACKNOWLEDGEMENTS

REFERENCES

1. Held, H.; Rengstl, A.; Mayer, D. *Acetic Anhydride and Mixed Fatty Acid Anhydrides: Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH: Weinheim; **2002**.
2. Tarbel, D.S. *Acc. Chem. Res.* **1969**, 2, 296.
3. Ogliarous, M.A.; Wolfe, J.F. *Synthesis of Carboxylic Acid, Esters and Their Derivatives*, John Wiley: New York; **1991**; p 198.
4. Rambacher, P.; Make, S. *Angew. Chem. Int. Ed.* **1968**, 7, 465.
5. Sandler, S.R.; Karo, W. *Organic Functional Group Preparation*, Academi Press: New York; **1972**.
6. Kazemi, F.; Kiasat, R. *Phos. Sulf. Silicon* **2003**, 178, 2287.
7. Adduci, J.M.; Ramirez, R.S. *Org. Prep. Proced. Int.* **1970**, 2, 321.
8. Kazemi, F.; Sharghi, H.; Nasseri, M. A. *Synthesis* **2004**, 205.
9. Kawamura, Y.; Sato, Y.; Horie, T.; Tsukayama, M. *Tetrahedron Lett.* **1997**, 38, 7893.
10. Kocz, R.; Roestamadji, J.; Mobashery, S. *J. Org. Chem.* **1994**, 59, 2913.
11. Park, Y.D.; Kim, J.J.; Kim, H.K.; Cho, S.D.; Kang, Y.J.; Park, K.H.; Lee, S.G.; Yoon, Y.J. *Synth. Commun.* **2005**, 35, 371;
12. Kim, J.J.; Park, Y.D.; Lee, W.S.; Cho, S.D.; Yoon, Y.J. *Synthesis* **2003**, 1517.

13. Kita, Y.; Akia, S.; Ajimura, N.; Yoahigi, M.; Tsugoshi, T.; Yasuda, H.; Tamura, Y. *J. Org. Chem.* **1986**, 51, 4150.
14. Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, 64, 6984.
15. Kaminki, Z.J.; Kolesinka, B.; Malgorzata, M. *Synth. Commun.* **2004**, 34, 3349.
16. Chen, F.; Benoiton, N.L. *Synthesis* **1970**, 710.
17. Kim, Y.H.; Kim, K.; Park, Y.J. *Tetrahedron Lett.* **1990**, 31, 3893.
18. Keshavamurthy, K.S.; Vankar, Y.D.; Dhar, D.N. *Synthesis* **1982**, 506.
19. Clarke, P.A.; Kayaleh, N.E.; Smith, M.A.; Baker, J.R.; Bird, S.J.; Chan, C. *J. Org. Chem.* **2002**, 67, 5226.
20. Kim, J.; Jang, D.O. *Synth. Commun.* **2001**, 31, 395.
21. Burton, S.G.; Kaye, P.T. *Synth. Commun.* **1989**, 19, 3331.
22. Liang, Y.; Jwo, J.J. *J. Mol. Catal. A: Chem.* **2001**, 170, 57.
23. Hajipour, A.R.; Mazloumi, G. *Synth. Commun.* **2002**, 32, 23.
24. Fukuoka, S.; Takimoto, S.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, 28, 4711.
25. Leadbeater, N.E.; Scott, K.A. *J. Org. Chem.* **2000**, 65, 4770.
26. Srivastava, R.R.; Kabalba, G.W. *Tetrahedron Lett.* **1992**, 33, 593.
27. Dhimitruka, I.; SantaLucia, J.J. *Org. Lett.* **2006**, 8, 47.
28. Hu, Y.; Wang, J.X.; Li, S. *Synth. Commun.* **1997**, 27, 243.
29. Martin, J.O. *Acc. Chem. Res.* **2004**, 37, 506.
30. Maruoka, K. *Org. Process Res. Dev.* **2008**, 12, 679.
31. Yang, H.M.; Huang, C.C. *Ind. Eng. Chem. Res.* **2007**, 46, 7915.
32. Jones, A.R. *Quaternary Ammonium Salts: Their Use in Phase Transfer Catalysis (Best Synthetic Methods)*, Elsevier: Amsterdam; **2001**.
33. Hamilton, G.L.; Kanai, T.; Toste, F.D. *J. Am. Chem. Soc.* **2008**, 130, 14984.
34. Hu, Y.L.; Wei, W.; Liu, Q.F.; Lu, M. *Bull. Chem. Soc. Ethiop.* **2010**, 24, 277.
35. Arata, K. *Appl. Catal. A: Gen.* **1996**, 146, 3.
36. Corma, A. *Chem. Rev.* **1995**, 95, 559.
37. Li, X.; Nagaoka, K.; Simon, L.J.; Lercher, J.A. *J. Catal.* **2005**, 230, 214.