$H_3PW_{12}O_{40}$-SiO_2 and Amberlyst 15: Two Efficient Heterogeneous Catalysts for Synthesis of *N*-Acylsulfonamides under Solvent-free Conditions

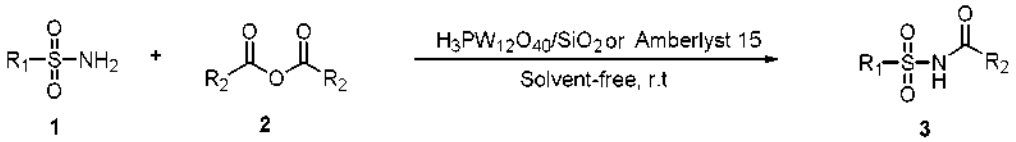
Liqiang Wu,* Chunguang Yang, Chong Zhang, and Limin Yang

*School of Pharmacy, Xinxiang Medical University, Xinxiang, Henan 453003, P. R. China. *E-mail: wliq1974@sohu.com*
Received February 5, 2009, Accepted May 28, 2009

Key Words: *N*-Acylsulfonamides, $H_3PW_{12}O_{40}$-SiO_2, Amberlyst 15, Solvent-free

The synthesis of *N*-acylsulfonamides has been considered of great interest to organic chemists owning to their diverse biological activities as precursors of therapeutic agents for Alzheimer's disease,[1] antibacterial and carbonic anhydrase II inhibitory,[2] antagonists for Angiotensin II[3] and Leukotriene D-receptors.[4] The most common methods for the *N*-acylation of sulfonamides are the reaction of parent sulfonamides with acylchlorides or anhydrides in the presence of trialkyl amines, pyridine,[5] H_2SO_4,[6] Lewis acids[7] or heterogeneous solid acid.[2,8] Other methods involve direct coupling of sulfonamides with carboxylic acids using condensing agents such as carbodiimides (EDC or DCC) or *N,N'*-carbonyldiimidazole.[9] However, most of these procedures have signicant drawbacks such as long reaction times, low yields, harsh reaction conditions, tedious workup procedures, or use of environmentally toxic reagents or media. Thus, there is still need of a simple and general procedure for the *N*-acylation of sulfonamides under mild conditions.

In recent years, the use of heterogeneous catalysts has received considerable interest in various disciplines including organic synthesis. They are advantageous over their homogeneous counterparts due to the prime advantage that in most



1 **2** **3**

Scheme 1

Table 1. Preparation of *N*-acylsulfonamides catalyzed by $H_3PW_{12}O_{40}$-SiO_2 or Amberlyst 15[a]

Entry	R^1	R^2	Products	Catalyst[b]	Time (min)	Yield (%)	m.p.(°C) (lit. m.p.)[ref]
1	Ph	Me	**3a**	i ii	8 8	95 (94, 92, 95, 94)[c] 94 (92, 94, 91, 92)[c]	124-126 (122-124)[8a]
2	Ph	*i*-Pr	**3b**	i ii	5 5	97 96	120-121
3	Ph	Ph	**3c**	i ii	40 40	90 88	142-143 (146)[13]
4	4-Me-C_6H_5	Me	**3d**	i ii	8 8	94 93	133-134 (138-140)[8a]
5	4-MeO-C_6H_5	Me	**3e**	i ii	8 8	87 89	188-190
6	4-NO_2-C_6H_5	Me	**3f**	i ii	8 8	84 85	193-194 (197-199)[7]
7	4-Cl-C_6H_5	Me	**3g**	i ii	8 8	90 91	189-190 (192-194)[8a]
8	Me	Me	**3h**	i ii	5 5	86 87	96-97
9	Me	*i*-Pr	**3i**	i ii	5 5	79 75	93-94 (97-99)[8b]
10	Me	Ph	**3j**	i ii	30 30	89 87	146-148 (148-153)[14]

[a]All the products were characterized by their spectral properties (^{1}H NMR, ^{13}C NMR) and element analysis. [b]Catalyst i: 60% $H_3PW_{12}O_{40}$-SiO_2 (2 mol%). ii: Amberlyst 15 (2 mol%). [c]Isolated yields after recycling of catalyst.

of the cases the catalyst can be recovered easily and reused.[10] Tungstophosphoric acid supportedon silica gel ($H_3PW_{12}O_{40}$-SiO_2) and Amberlyst 15 have been used as efficient heterogeneous catalysts for many organic transformations because of their low cost, ease of preparation, catalyst recycling, and ease of handling.[11,12] We now report a simple and efficient route to synthesis of *N*-acylsulfonamides using $H_3PW_{12}O_{40}$-SiO_2 or Amberlyst 15 as an efficient and environmentally benign catalyst under solvent-free conditions (see Scheme 1).

First, to optimize the amount of catalyst, the reaction of benzenesulfonamide (1 mmol) with acetic anhydride (2 mmol) under solvent-free conditions at room temperature was selected as a model. The best result was obtained with 2 mol% $H_3PW_{12}O_{40}$-SiO_2 (60%, w/w) or Amberlyst 15. Higher amounts of catalyst did not lead to significant change in the reaction yields.

Based on the optimized reaction conditions, a range of *N*-acylsulfonamides was synthesized by the reaction of sulfonamide (**1**, 1 mmol) with anhydride (**2**, 2 mmol). The reaction proceeded at room temperature within 45 minutes in excellent yields after the addition of the acid catalyst $H_3PW_{12}O_{40}$-SiO_2 or Amberlyst 15 (see Table 1). In these experiments, the catalyst was isolated by filtration and could be reloaded with fresh reagents for further runs, thus, recyclization of catalyst is possible without significant loss of activity (Table 1, entry 1). In addition, we noticed also that the yields of products were almost similar with these two catalysts.

In order to show the merit of the presented protocol, the model reaction between benzenesulfonamide of acetic anhydride was described, and different catalysts such as H_2SO_4, Fe-exchanged montmorillonite K10 (K10-FeO), silica sulfuric acid (SSA), silica chloride (SiO_2-Cl), $ZnCl_2$, I_2 were subjected to the reaction (Table 2). All the reactions were run in the same conditions, and similar amounts of catalysts (2 mol%) were used. Table 2 revealed that $H_3PW_{12}O_{40}$-SiO_2 and Amberlyst 15 were equally efficient and environmentally benign catalysts in the synthesis of *N*-acylsulfonamides.

Experimental Section

General procedure for the preparation of 3. To a mixture of sulfonamide (1 mmol), anhydride (2 mmol), 60% $H_3PW_{12}O_{40}$-SiO_2 (2 mol%) or Amberlyst 15 (2 mol%) was added. The mixture was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction (TLC), 10 mL EtOAc was added to the reaction mixture and the catalyst was recovered by filtered. The organic layer was dried over $MgSO_4$, the solvent was evaporated and puried by column chromatography on silica gel using EtOAc-petroleum ether as elue to afford pure *N*-acylsulfonamides in 75-97% yields.

***N*-(Phenylsulfonyl)isobutyramide (3b).** White solid, m.p. 120-121 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.20 (br s, 1H), 8.12 (d, J = 6.6 Hz, 2H), 7.82 (t, J = 6.6 Hz, 1H), 7.64 (t, J = 7.3 Hz, 2H), 2.58 (m, 1H), 1.02 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.4, 136.37, 130.8, 128.2, 128.1, 125.0, 124.8, 36.2, 20.4, 20.2; Anal. calcd for $C_{10}H_{13}NO_3S$: C 52.85, H 5.77, N 6.16; found: C 52.68, H 5.52, N 6.22.

***N*-(4-Methoxyphenylsulfonyl)acetamide (3e).** White solid, m.p. 188-190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.26 (br s, 1H), 8.10 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 3.82 (s, 3H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.2, 165.3, 130.1, 126.0, 125.8, 111.2, 110.8, 57.2, 22.4; Anal. calcd for $C_9H_{11}NO_4S$: C 47.15, H 4.84, N 6.11; found: C 46.96, H 4.70, N 6.18.

Table 2. Comparison of the effect of catalysts in synthesis of *N*-(phenylsulfonyl)acetamide

Entry	Catalysis	Yield/%
1	H_2SO_4	28
2	K10-FeO	42
3	SSA	83
4	SiO_2-Cl	80
5	$ZnCl_2$	88
6	I_2	41
7	60% $H_3PW_{12}O_{40}$-SiO_2	95
8	Amberlyst 15	94

[a]Benzenesulfonamide: acetic anhydride = 1: 2; reactions executed at room temperature for 8 min.

Acknowledgments. We are pleased to acknowledge the financial support from Xinxiang Medical University (No. 04GXLP05)

Reference

1. Hasegawa, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 423.
2. Massah, A. R.; Adibi, H.; Khodarahmi, K.; Abiri, R.; Majnooni, M. B.; Shahidi, S.; Asadi, B.; Mehrabi, M.; Zolgol, M. A. *Bioorg. Med. Chem.* **2008**, *16*, 5465.
3. Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Chen, T. B.; O'Malley, S. S.; Zingaro, G. J.; Siegl, P. K. S.; Kivlighn, S. D.; Lotti, V. J.; Chang, R. S. L.; Greenless, W. J. *J. Med. Chem.* **1994**, *37*, 4464.
4. Musser, J. H.; Kreft, A. F.; Bender, R. H. W.; Kubrak, D. M.; Grimes, D.; Carlson, R. P.; Hand, J. M.; Chang, J. *J. Med. Chem.* **1990**, *33*, 240.
5. Kondo, K.; Sekimoto, E.; Miki, K.; Murakami, Y. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2973.
6. Martin, M. T.; Roschangar, F.; Eaddy, J. F. *Tetrahedron Lett.* **2003**, *44*, 5461.
7. Reddy, C. R.; Mahipal, B.; Yaragorla, S. R. *Tetrahedron Lett.* **2007**, *48*, 7528.
8. (a) Singh, D. U.; Singh, P. R.; Samant, S. D. *Tetrahedron Lett.* **2004**, *45*, 4805; (b) Massah, A. R.; Momeni, A. R.; Dabagh, M. *Synth. Commun.* **2007**, *38*, 265.
9. Wang, Y.; Soper, D. L.; Dirr, M. J.; Delong, M. A.; De, B.; Wos, J. A. *Chem. Pharm. Bull.* **2000**, *48*, 1332.
10. Clark, J. H. *Acc. Chem. Res.* **2002**, *35*, 791.
11. (a) Mirjalili, B. B. F.; Zaghaghi, Z. *J. Chin. Chem. Soc.* **2008**, *55*, 694; (b) Meuzelaar, G.; Maat, L.; Sheldon, R.; Kozhevnikov, I. V. *Catal. Lett.* **1997**, *45*, 249; (c) Kozhevnikova, E. F.; Rafiee, E.; Kozhevnikov, I. V. *Appl. Catal.* **2004**, *A260*, 25; (d) Mao, J.; Nakajo, T.; Okuhara, T. *Chem. Lett.* **2002**, 1104.
12. (a) Das, B.; Banerjee, J. *Chem. Lett.* **2004**, *33*, 960; (b) Ramesh, C.; Banerjee, J. R.; Pal, B. D. *Adv. Synth. Catal.* **2002**, *345*, 557; (c) Feng, X.-L.; Guan, C.-J.; Zhao, C.-X. *Synth. Commun.* **2004**, *34*, 487; (d) Farhanullah.; Ashoke, S.; Maulik, P. R.; Ram V. J. *Tetrahedron Lett.* **2004**, *45*, 5099; (e) Solladie-Cavallo, A.; Lupattelli, P.; Bonini, C. *J. Org. Chem.* **2005**, *70*, 1605; (f) Das, B.; Thirupathi, P.; Mahender, I.; Reddy, V. S.; Rao, Y. K. *J. Mol. Catal. A: Chem.* **2006**, *255*, 233; (g) Ko, S.-K.; Yao, C.-F. *Tetrahedron Lett.* **2006**, *47*, 8827.
13. Yijima, C.; Hino, F.; Suda, K. *Synthesis* **1981**, 610.
14. Oh, S. W. *J. Photosci.* **2005**, *12*, 63.