Turk J Chem
31 (2007) , 611 – 616.

A Convenient and Efficient Synthesis of *N*-Acylsulfonamides in the Presence of Silica Phosphoric Acid under Heterogeneous and Solvent-Free Conditions

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Received 07.02.2007

Reaction of sulfonamides with carboxylic acid anhydrides and chlorides in the presence of silica phosphoric acid provided *N*-acyl sulfonamides in good to high yields. All reactions were performed under mild conditions in solvent-free and heterogeneous systems and the products were obtained in high purity after a simple work-up. Silica phosphoric acid could be reused for 3 times without visible loss of activity.

Key Words: *N*-acylsulfonamide, solvent-free, silica phosphoric acid, heterogeneous condition, *N*-acylation.

Introduction

Solid acids have been used in organic reactions instead of liquid acids due to their advantages such as ease of handling, decreasing reactor and plant corrosion problems, and environmentally safe disposal.[1,2] Wastes and by-products can be minimized or avoided by developing cleaner synthesis routes.[3] In addition, there is current research and general interest in heterogeneous systems because of their importance in industry and in developing technologies.[4] Among the solid acids, silica resin with acid functional moieties has found wide application in organic reactions from different views.[5] Solid silica chloride has been used as an efficient heterogeneous catalyst in functional group transformation reactions.[6−11] Zolfigol et al. reported the first example of silica solid acid with phosphoric acid moiety. They prepared this catalyst with the addition of H_3PO_4 to silica chloride.[12] In view of this and in connection with our interest in sulfonamide synthesis,[13] herein we report the silica phosphoric acid catalyzed *N*-acylation of sulfonamides for the synthesis of *N*-acylsulfonamides.

The most practical methods for the synthesis of *N*-acylsulfonamides, as an important class of pharmacological agents,[14−17] involve the reaction of parent sulfonamide with acyl chlorides or anhydrides in basic conditions.[18−21] Acylation of sulfonamides with concentrated H_2SO_4 in carboxylic acid anhydride as

solvent[22] or in acetonitrile[23] are some of the less common reports mentioning this transformation under acidic conditions. Another approach utilizes carboxylic acids along with condensing agents such as carbodiimides (EDC, DCC) and *N*,*N*'-carbonyldiimidazole.[15,24,25] However, most of the reported methods suffer from one or more of the following disadvantages: long reaction time, vigorous reaction conditions, the occurrence of side reactions especially formation of bis acylated by-product, use of expensive or unavailable reagents, low yield of product, and tedious work-up. Thus, there is still a demand to develop new and mild methods for the *N*-acylation of sulfonamides in the presence of inexpensive and bench top reagents.

Results and Discussion

We report herein the results of *N*-acylation of different sulfonamides with some carboxylic acid anhydrides and chlorides in the presence of silica phosphoric acid under solvent-free and heterogeneous conditions. In a simple procedure, a mixture of reactants was vigorously stirred at 80 °C under solvent-free conditions or refluxed in *n*-hexane for the appropriate time. The progress of the reactions was monitored by TLC and the products were isolated in good to high yield after an easy work-up.

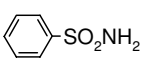
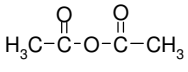
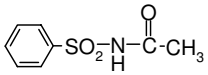
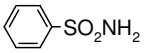
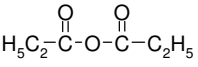
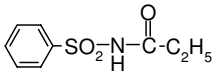
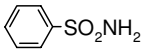
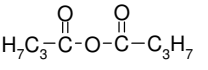
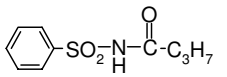
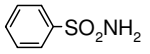
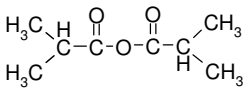
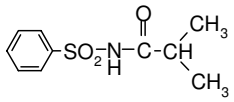
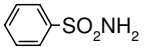
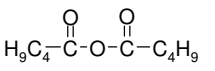
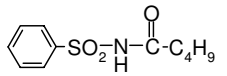
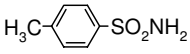
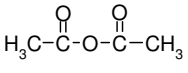
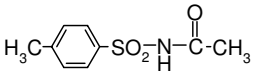
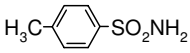
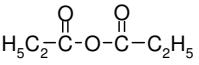
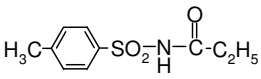
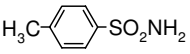
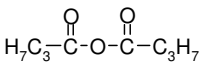
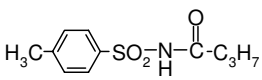
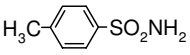
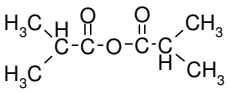
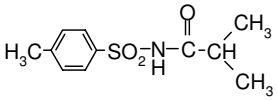
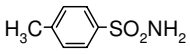
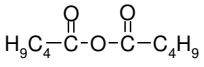
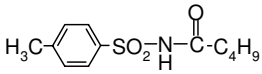
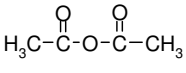
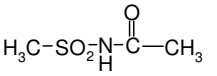
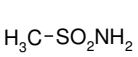
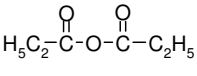
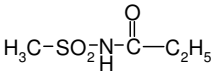
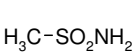
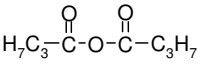
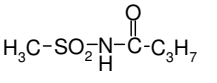
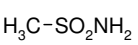
At first, the reaction was optimized with respect to solvent, amount of catalyst, and reaction time. In order to find the best solvent, the reaction of benzensulfonamide with acetic anhydride was carried out in different solvents. *n*-Hexane yielded the smallest amounts of side products and high yield, and was selected as the solvent for further study. Furthermore, we examined different ratios of sulfonamide, carboxylic acid anhydride, or chloride. When the molar ratio of sulfonamide:acylating agent was 1:2 in the presence of 0.3 g of silica phosphoric acid, the reaction gave the best results under both *n*-hexane and solvent-free conditions.

In order to test the general applicability of our reaction, benzensulfonamide, *p*-toluensulfonamide, and methansulfonamide were subjected to *N*-acylation with different kinds of carboxylic acid anhydrides and chlorides under both *n*-hexane and solvent-free conditions. As shown in Tables 1 and 2, several structurally varied sulfonamides and acylating agents underwent clean and remarkably fast *N*-acylation reactions. It seems that there was no steric bulk effect from the substituents at anhydride moiety, since isobutanoic anhydride could be applied as an efficient candidate for *N*-acylation of different sulfonamides to offer the expected *N*-acylsulfonamides in excellent yields in both heterogeneous and solvent-free conditions. On the other hand, the comparison between the results obtained in solution and those under solvent-free conditions showed that the reaction proceeded faster under the latter. Therefore, omission of the solvent makes an easy work-up procedure and increases the rate of reaction.

Silica phosphoric acid is immiscible with non-polar organic compounds or solvents. Thus, recovery of catalyst is convenient when a non-polar solvent is used as medium. In the present method, after the reaction, by simple filtration, the catalyst was recovered. To rule out the possibility of catalyst leaching, the activity of the recovered catalyst in each reaction was investigated carefully. The experimental results revealed that more than 90% of the silica phosphoric acid could be recovered. In *N*-acylation of benzensulfonamide with acetyl chloride or acetic anhydride, silica phosphoric acid could be reused 3 times without visible loss of activity.

In conclusion, silica phosphoric acid was found to be a recyclable catalyst for the *N*-acylation of various sulfonamides with both carboxylic acid anhydrides and chlorides under solvent-free and heterogeneous conditions. In addition, the method has advantages in terms of low cost and availability of the reagents, high yield and purity of products, short reaction times, operational simplicity, and easy work-up. This method is a green chemistry approach to the preparation of *N*-acyl sulfonamides.

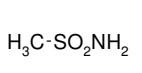
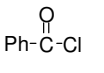
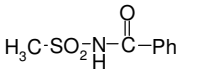
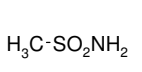
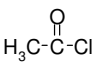
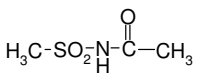
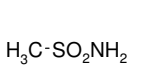
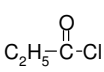
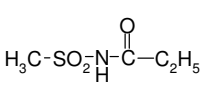
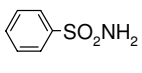
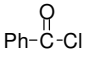
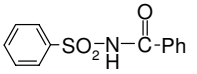
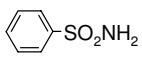
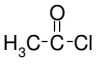
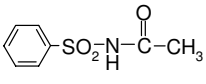
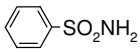
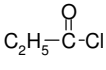
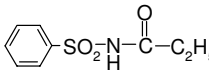
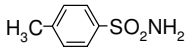
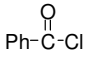
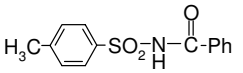
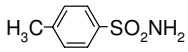
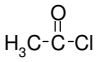
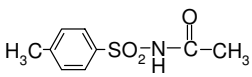
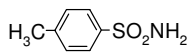
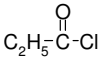
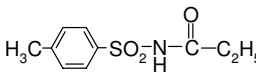
Table 1. *N*-acylation of sulfonamides with carboxylic acid anhydride under *n*-hexane or solvent-free condition.

Entry	Sulfonamide	Carboxylic acid anhydride	Product	Solvent-free[a]		*n*-Hexane[b]	
				Time(min)	Yield(%)	Time(min)	Yield(%)
1				60	85	55	80
2				20	90	25	85
3				25	85	30	80
4				20	97	25	95
5				30	85	35	80
6				120	87	90	95
7				25	83	30	80
8				30	87	35	85
9				25	97	25	97
10				35	84	40	80
11				50	83	60	80
12				15	87	20	82
13				15	85	20	80
14				15	98	20	96
15				25	80	30	80

a) 80 °C

b) Reflux

Table 2. *N*-acylation of sulfonamides with carboxylic acid chlorides under *n*-hexane or solvent-free condition.

Entry	Sulfonamide	carboxylic acid chloride	Product	Solvent-free[a]		*n*-Hexane[b]	
				Time(min)	Yield(%)	Time(min)	Yield(%)
1				25	89	35	80
2				35	80	60	85
3				20	85	60	80
4				45	90	40	82
5				110	82	130	80
6				150	85	110	80
7				110	82	120	80
8				120	90	240	60
9				70	87	90	75

a) 80 °C
b) Reflux

Experimental

All chemicals were purchased from Merck and Fluka. Silica phosphoric acid was prepared as described previously.[12] The products were characterized by comparing the physical data with those of known samples or by their spectral data. Infrared spectra were recorded on a Nicolet (impact 400D model) FT IR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DRX 300 Avance spectrophotometer in DMSO-d_6 as the solvent and TMS as internal standard. Column chromatography was performed using silica gel 60 (230-400 mesh). All yields refer to isolated yields.

General procedure for N-acylation of sulfonamides under solvent-free conditions: To a vigorously stirred mixture of sulfonamide (1 mmol) and silica phosphoric acid (0.3 g) was added carboxylic acid chloride (2 mmol) or carboxylic acid anhydride (2 mmol) at 80 °C in 2 portions. The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate (20 mL) was added and the solid catalyst was removed by filtration. The solvent was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (60-120 mesh, EtOAc-petroleum ether) or by recrystallization (toluene or ethyl acetate-*n*-hexane) to afford the corresponding

N-acyl sulfonamide in good to high yields.

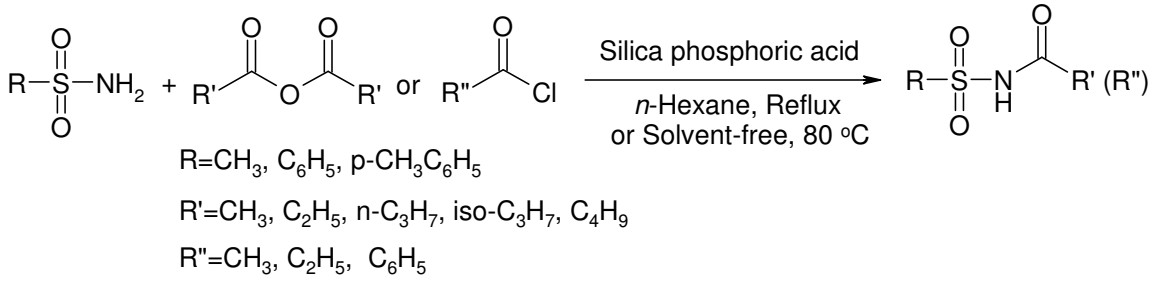
General procedure for N-acylation of sulfonamides in n-hexane: A mixture of sulfonamide (1 mmol), carboxylic acid chloride (2 mmol), or carboxylic acid anhydride (2 mmol) was refluxed in *n*-hexane (5 mL) in the presence of silica phosphoric acid (0.3 g) for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was filtered off and water (10 mL) was added and extracted with ethyl acetate (2 × 10 mL). The solvent was evaporated and the crude product was purified according to the solvent-free procedure. Spectral data of some isolated *N*-acylsulfonamides are as follows:

N-isobutanoyl-4-methyl benzensulfonamide (Table 1, entry 9): mp; 111-113 °C, IR υ (cm^{-1}) 3259, 1731, 1329, 1171; ^{1}H-NMR (DMSO-d_6): δ 0.92 (d, J = 6.8 Hz, 6H), 2.38 (s, 3H), 2.41-2.46 (m, 1H), 7.4 (d, J = 7.8 Hz, 2H), 7.78 (d, J = 7.8 Hz, 2H), 11.99 (s, 1H); ^{13}C-NMR (DMSO-d_6): δ 16.92, 19.57, 32.75, 125.97, 128.03, 135.03, 142.6, 173.7.

N-propanoyl methansulfonamide (Table 1, entry 12): mp; 70-72 °C, IR υ(cm^{-1}) 3143, 1687, 1343, 1158; ^{1}H-NMR (DMSO-d_6): δ 0.99 (t, J = 7.5 Hz, 3H), 2.27 (q, J = 7.5 Hz, 2H), 3.22 (s, 3H), 11.63 (s, 1H); ^{13}C-NMR (DMSO-d_6): δ 8.84, 19.16, 43.58, 173.72.

N-butanoyl methansulfonamide (Table 1, entry 13): mp; 68-70 °C, IR υ(cm^{-1}) 3203, 1700, 1330, 1151, ^{1}H-NMR (DMSO-d_6): δ 0.86 (t, J = 7.3 Hz, 3H), 1.53 (sext, J = 7.3 Hz, 2H), 2.23 (t, J = 7.3 Hz, 2H), 3.22 (s, 3H), 11.64 (s, 1H); ^{13}C-NMR (DMSO-d_6): δ 13.22, 17.50, 37.14, 40.88, 172.46.

N-isobutanoyl methansulfonamide (Table 1, entry 14): mp; 97-99 °C, IR υ(cm^{-1}) 3213, 1717, 1329, 1158; ^{1}H-NMR (DMSO-d_6): δ 1.03 (d, J = 6.8 Hz, 6H), 1.53 (sept, J = 6.8 Hz, 1H), 3.22 (s, 3H), 11.64 (s, 1H); ^{13}C-NMR (DMSO-d_6): δ 19.05, 34.73, 41.32, 176.85.



Scheme. *N*-acylation of sulfonamides with carboxylic acid anhydrides or chlorides.

Acknowledgments

We thank Dr. Taki for his kind help and also partial support of Islamic Azad University, Shahreza Research Council.

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