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Synthesis, in vitro antibacterial and carbonic anhydrase II inhibitory activities of *N*-acylsulfonamides using silica sulfuric acid as an efficient catalyst under both solvent-free and heterogeneous conditions

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Abstract—Silica sulfuric acid catalyzes efficiently the reaction of sulfonamides with both carboxylic acid anhydrides and chlorides under solvent-free and heterogeneous conditions. All the reactions were done at room temperature and the *N*-acylsulfonamides were obtained with high yields and purity via an easy work-up procedure. This method is attractive and is in a close agreement with green chemistry. These compounds were also investigated for antibacterial activity, including Gram-positive cocci and Gram-negative bacilli, and carbonic anhydrase II inhibitory activity.

1. Introduction

N-Acylsulfonamides have received considerable attention due to their diverse biological activities as precursors of therapeutic agents for Alzheimer's disease,[1] antibacterial inhibitors of tRNA synthetases,[2] antagonists for Angiotensin II,[3] and Leukotriene D_4-receptors.[4]

Most N-acylation of sulfonamides has utilized carboxylic acid chlorides or anhydrides in the presence of trialkylamines, pyridine,[5,6] or alkali hydroxides[7–9] in appropriate solvent. The occurrence of the side reaction especially formation of bis-acylated by product, is the most important disadvantage of the described methods. Direct coupling of sulfonamides with carboxylic acids has used condensing agents such as carbodiimides (EDC and DCC) and 1,1′-carbonyl diimidazole.[2,10] Recently, Katrizky et al. were reported N-acylation of sulfonamides using *N*-acyl benzotriazole as an acylating agent.[11] However, some of the above-mentioned methods suffer from one or more of the following disadvantages: long reaction times, vigorous reaction conditions, use of expensive or unavailable reagents, low yield of product, and tedious work-up.

There are few limited procedures that have described the formation of *N*-acylsulfonamides under protic acid conditions.[12,13] From the standpoint of environmental demand for chemical processes, much attention has been paid to the development of solid acidic reagents for organic functional groups transformations.[14] On the other hand, any reduction in the amount of protic acid needed

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Keywords: *N*-Acylsulfonamides; Silica sulfuric acid; Solvent-free; Antibacterial activity; Carbonic anhydrase II inhibitor.

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and/or any simplification in handling procedures is required for risk reduction, economic advantage and environmental protection. 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.

At least 14 different cytosolic (CA I, II, O, and VII) and membrane-bound (CA IV, IX, XII, and XIV) carbonic anhydrase (E.C. 4.2.1.1) isoforms were isolated in higher vertebrates. These enzymes catalyze a very simple physiological reaction, the interconversion between carbon dioxide and bicarbonate ion, and are thus involved in crucial physiologic processes connected with respiration and transport of CO_2/bicarbonate between metabolizing tissues and lungs, pH, and CO_2 homeostasis, electrolyte secretion in a variety of tissues/organs, biosynthetic reactions, bone resorption, calcification, tumorigenicity, and many other physiologic or pathologic processes. Several important physiologic and physio-pathologic functions played by many carbonic anhydrase isoezymes, are strongly inhibited by aromatic and heterocyclic sulfonamides as well as by inorganic, metal complexing anions.[15]

Since the catalytic and inhibition mechanisms of the CA isoenzymes have been understood in detail, the design of potent specific isoenzymes and organ-selective inhibitors can be important due to their various clinical applications. Several sulfonamide compounds that interact with CA have recently been synthesized and applied as antiglucoma, antiepileptic, and for the treatment of other neurological disorders, anti cancer and also as diagnostic tools in PET and MRI. The CA II is present in some cells of virtually all tissue types and plays a vital role in respiration and acid–base balance.[16]

Recently, silica sulfuric acid (SSA) has been introduced as a novel solid inorganic acidic proton source catalyst[17] by the reaction of silica gel and chlorosulfonic acid for the various functional group transformations.[18–29] In continuation of our studies in this regard,[29] we report our efforts toward a new solvent-free and heterogeneous procedure for the synthesis of *N*-acylsulfonamides with carboxylic acid anhydrides and chlorides in the presence of a catalytic amount of silica sulfuric acid and evaluation of their in vitro antibacterial activity. Furthermore, the inhibitory effects of *N*-acylsulfonamides were tested on the cytosolic human carbonic anhydrase II in the micro-to-nanomolar range.

2. Chemistry

2.1. Optimization of reaction conditions

A variety of reaction conditions were performed to optimize the reaction. To illustrate the need of catalyst for these reactions, an experiment was conducted in which the reaction of benzensulfonamide and acetic anhydride or acetyl chloride was studied in the absence of SSA. The reaction did not occur, even after 24 h in the absence of the catalyst. Obviously, the SSA is an essential component of the reaction. Then a similar reaction was studied in the presence of various amounts of SSA. We have observed that the reaction between benzensulfonamide (1 mmol), acetic anhydride or acetyl chloride (2 mmol), and silica sulfuric acid (0.008 g) was completed after 8–25 min in a solvent-free condition at room temperature. For comparing the solvent-free results with solvent added ones, the reaction of benzensulfonamide with acetic anhydride and also acetyl chloride was carried out under various solvents. Chloroform led to the smallest amount of side products with high yields and it was selected as the solvent for further study.

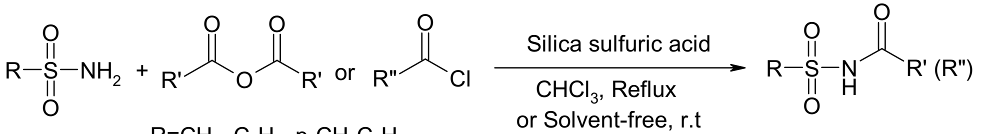
2.2. Generality of silica sulfuric acid catalyzed N-acylation of sulfonamides

To explore the scope and limitation of the described reactions, we studied the reaction of benzensulfonamide, 4-methylbenzensulfonamide, and methansulfonamide with several aliphatic and aromatic carboxylic acid anhydrides or chlorides in the presence of SSA. The reaction proceeded very efficiently in all the cases. As it is shown in Table 1, several structurally varied sulfonamides and acylating agents underwent clean and remarkably fast N-acylation reaction. The aliphatic anhydride with a long chain, like pentanoic anhydride (Table 1, entries **1e**, **1k**, and **1q**) could be used as effectively as one with a short chain. Also, it seemed that there was no steric bulk effect from the substituents at the 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 (Table 1, entries **1d**, **1j**, and **1p**). Carboxylic acid anhydrides were found to be more reactive than carboxylic acid chlorides. These results show that the acylinium ion was formed and then reacted with sulfonamide. This fact was further supported by N-acylation of sulfonamides with trifluoroacetic anhydride. For example, the reaction of benzensulfonamide with trifluoroacetic anhydride did not proceed considerably and only 10% of the product was obtained after 8 h. Comparison between the results obtained in solution and those under solvent-free conditions shows that the reaction proceeded faster in solvent-free conditions. Therefore, omitting of solvent (i.e., solvent-free conditions) makes an easy work-up procedure and increases the rate of reaction.

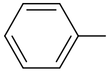
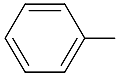
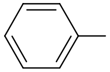
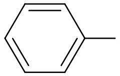
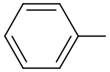
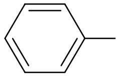
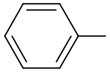
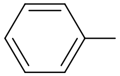
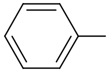
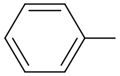
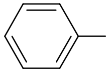
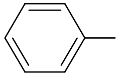
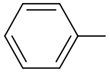
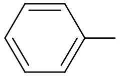
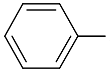
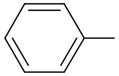
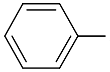
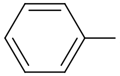
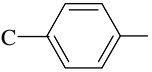
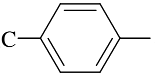
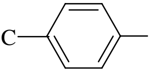
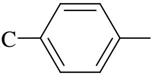
2.3. Chemoselectivity and large-scale use

In order to show the chemoselectivity of the method for the reaction of sulfonamides with different carbonyl groups, we designed a number of competitive reactions. As shown in Scheme 1 selectivity of the method is very promising and discriminates between different CO functionalities. In fact, sulfonamide reacted with carbonyl group that formed more stable acylinium ion. We have also conducted a similar reaction on a large-scale operation. For this purpose benzensulfonamide (1.56 g, 10 mmol) was reacted with acetic anhydride (2.04 g, 20 mmol) in the presence of a catalytic amount of SSA (0.08 g). The reaction proceeded very fast in less than 8 min to produce *N*-acetyl sulfonamide in 88% yield.

Table 1. N-Acylation of sulfonamides in chloroform or solvent-free conditions

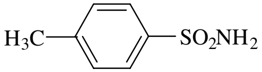
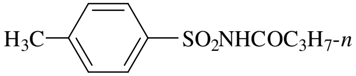
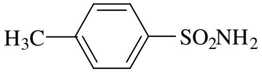
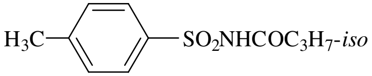
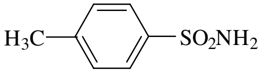
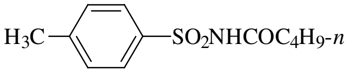
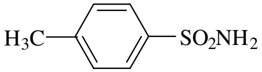
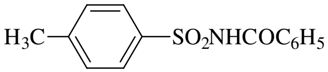
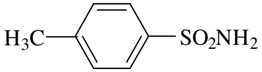
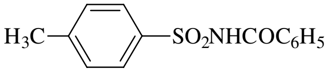
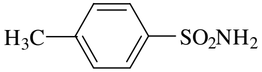
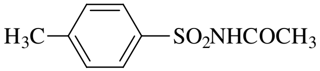
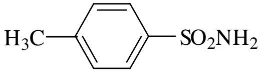
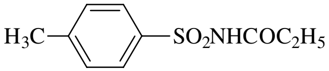


R=CH_3, C_6H_5, p-$CH_3C_6H_5$
R'=CH_3, C_2H_5, n-C_3H_7, iso-C_3H_7, n-C_4H_9, C_6H_5
R"=CH_3, C_2H_5, C_6H_5

Entry	Sulfonamide	Acylating agent	Product	Solvent-free[a]		CHCl$_3$[b]	
				Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]
1a	 SO_2NH_2	$H_3COOCOCH_3$	 $SO_2NHCOCH_3$	8	85	45	80
1b	 SO_2NH_2	$H_5C_2COOCOC_2H_5$	 $SO_2NHCOC_2H_5$	8	88	90	80
1c	 SO_2NH_2	n-$H_7C_3COOCOC_3H_7$-n	 $SO_2NHCOC_3H_7$-n	5	90	40	82
1d	 SO_2NH_2	iso-$H_7C_3COOCOC_3H_7$-iso	 $SO_2NHCOC_3H_7$-iso	8	95	45	94
1e	 SO_2NH_2	n-$H_9C_4COOCOC_4H_9$-n	 $SO_2NHCOC_4H_9$-n	10	90	70	80
1f	 SO_2NH_2	$H_5C_6COOCOC_6H_5$	 $SO_2NHCOC_6H_5$	90	88	180	80
1f	 SO_2NH_2	H_5C_6COCl	 $SO_2NHCOC_6H_5$	35	84	180	85
1a	 SO_2NH_2	H_3CCOCl	 $SO_2NHCOCH_3$	25	82	90	70
1b	 SO_2NH_2	H_5C_2COCl	 $SO_2NHCOC_2H_5$	20	84	50	82
1g	H_3C  SO_2NH_2	$H_3COOCOCH_3$	H_3C  $SO_2NHCOCH_3$	10	84	50	73
1h	H_3C  SO_2NH_2	$H_5C_2COOCOC_2H_5$	H_3C  $SO_2NHCOC_2H_5$	10	85	50	75

(*continued on next page*)

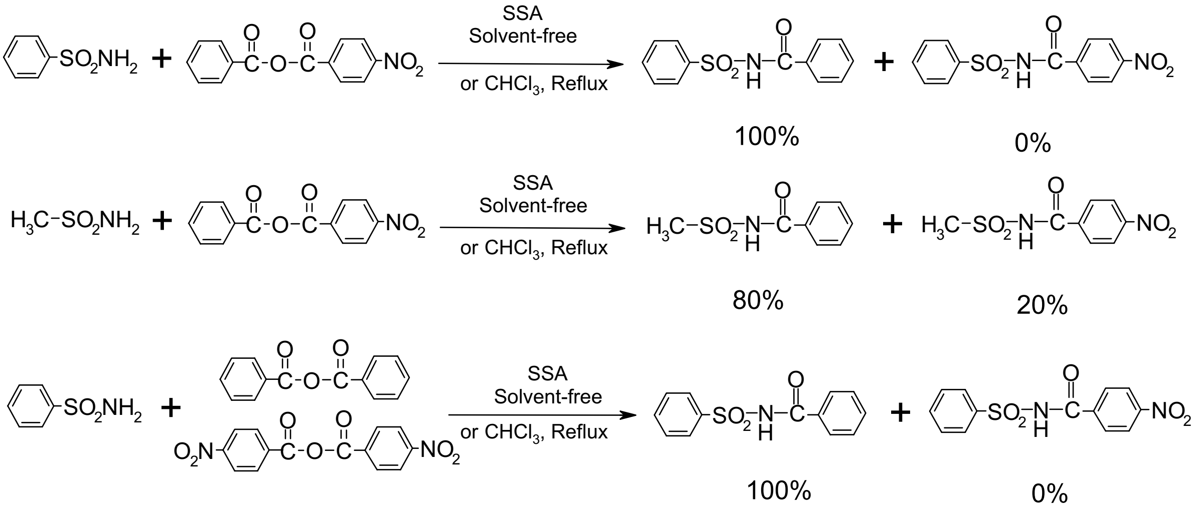
Table 1 (*continued*)

Entry	Sulfonamide	Acylating agent	Product	Solvent-free[a]		CHCl$_3$[b]	
				Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]
1i		n-$H_7C_3COOCOC_3H_7$-n		10	89	45	85
1j		iso-$H_7C_3COOCOC_3H_7$-iso		15	93	50	88
1k		n-$H_9C_4COOCOC_4H_9$-n		15	88	65	89
1l		$H_5C_6COOCOC_6H_5$		120	88	240	83
1l		H_5C_6COCl		35	95	135	83
1g		H_3CCOCl		25	90	75	78
1h		H_5C_2COCl		30	88	55	82
1m	H_3C–SO_2NH_2	$H_3COOCOCH_3$	H_3C–$SO_2NHCOCH_3$	5	80	30	70
1n	H_3C–SO_2NH_2	$H_5C_2COOCOC_2H_5$	H_3C–$SO_2NHCOC_2H_5$	5	78	20	75
1o	H_3C–SO_2NH_2	n-$H_7C_3COOCOC_3H_7$-n	H_3C–$SO_2NHCOC_3H_7$-n	3	78	10	80
1p	H_3C–SO_2NH_2	iso-$H_7C_3COOCOC_3H_7$-iso	H_3C–$SO_2NHCOC_3H_7$-iso	5	85	10	85
1q	H_3C–SO_2NH_2	n-$H_9C_4COOCOC_4H_9$-n	H_3C–$SO_2NHCOC_4H_9$-n	5	75	10	73
1r	H_3C–SO_2NH_2	$H_5C_6COOCOC_6H_5$	H_3C–$SO_2NHCOC_6H_5$	60	98	90	80
1r	H_3C–SO_2NH_2	H_5C_6COCl	H_3C–$SO_2NHCOC_6H_5$	20	94	120	78
1m	H_3C–SO_2NH_2	H_3CCOCl	H_3C–$SO_2NHCOCH_3$	20	81	55	70
1n	H_3C–SO_2NH_2	H_5C_2COCl	H_3C–$SO_2NHCOC_2H_5$	15	80	40	74

[a] At room temperature.

[b] Reflux conditions.

[c] Isolated yields.



Scheme 1. Chemoselectivity of the reaction.

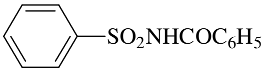
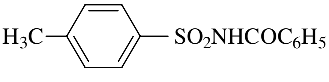
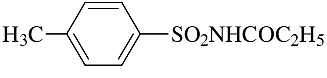
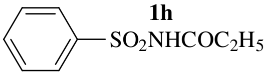
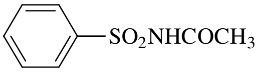
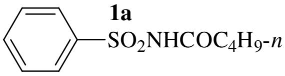
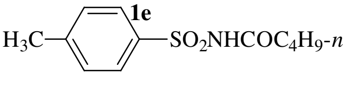
3. Results and discussion

3.1. In vitro antibacterial activity

The test compounds were evaluated for their antibacterial activity against three Gram-positive cocci (*Staphylococcus aureus* ATCC 25922, clinical strains of *S. aureus* and *Enterococcus* sp.) and three Gram-negative bacilli (*Pseudomonas aeruginosa* ATCC 27853, clinical strains of *Klebsiella pneumonia* and *Escherichia coli*) using conventional agar-dilution method.[30] The MICs (minimum inhibitory concentrations) values were determined by comparison to sulfamethoxazole as the reference drug and are presented in Table 2.

Turbidity of all the bacterial cultures was adjusted to 0.5 McFarland Standard by preparing bacterial suspension of 3–5 well-isolated colonies of the same morphological type selected from an agar plate culture. The cultures were further diluted 1000-fold to get an inoculum size

Table 2. In vitro antibacterial activity of *N*-acylsulfonamides against Gram-positive and Gram-negative bacteria (MICs in μg/mL)

Compound	*E. coli* (clinical isolated)	*E. faecium* (clinical isolated)	*K. pneumoniae* (clinical isolated)	*S. aureus* (clinical isolated)	*S. aureus* ATCC 25922	*P. aeruginosa* ATCC 27853
$H_3C–SO_2NHCOC_6H_5$ **1r**	256	256	500	256	500	500
 **1f**	256	256	256	500	256	256
 **1l**	64	128	256	256	256	256
 **1h**	128	64	500	128	64	500
 **1b**	256	64	256	256	128	500
Sulfamethoxazole	2	4	8	4	2	8
 **1a**	>1000	>1000	>1000	>1000	>1000	>1000
 **1e**	>1000	>1000	>1000	>1000	>1000	>1000
 **1k**	>1000	>1000	>1000	>1000	>1000	>1000

of 1.5×10^5 CFU/mL. The test compounds (50 mg) were dissolved in DMSO (0.5 mL) and the solution was diluted with water (4.5 mL) to get a stock solution of 10,000 mg/mL of each compound. Further progressive double dilution with Muller–Hinton broth was performed to obtain the required concentrations of 1000, 512, 256, 128, 64, 32, 16, 8, 4, and 2 μg/mL.[31] To ensure that the solvent had no effect on the bacterial growth, a control test was performed with a test medium supplemented with DMSO at the same dilutions as used in the experiment. Our results indicated that all the test compounds tested in this study demonstrated lower activity against both Gram-positive and Gram-negative microorganisms than the reference drug.

The standard antibiotic (sulfamethoxazole) was also diluted in the same manner. Each microwell in a series of 12 microwells was inoculated with 75 μL of the serial dilutions, and then 75 μL of the bacterial suspension was added. After overnight incubation at 37 °C, growth was surveyed. Data of MICs of the test compounds and the control drug are shown in Table 2.

3.2. Carbonic anhydrase II inhibitory activity

The enzyme identity and purity was tested through SDS-electrophoretic analysis and by comparing with commercial CA enzyme (Sigma), as a standard. The SDS–PAGE analysis is shown in Figure 1 (Inset), it clearly indicates the reasonable purity of the isolated enzyme.

The potency of test compounds (**1a**, **1b**, **1e**, **1f**, **1h**, **1k**, and **1r**) for the inhibition of CA II has been studied in vitro. Figure 1 summarizes the relative inhibitory potencies of the test compounds. Consistent with the published literature, the reference drug dorzolamide (with known IC_{50}) showed very good in vitro inhibitory properties against the isoenzyme II. Also as indicated in Figure 1, the strongest CA II inhibitor was compound **1h** (with potency comparable to that of dorzolamide). Contrary to compound **1h**, **1e**, and **1k** showed relatively weaker inhibitory effects in the CA assay. The potencies for CA II inhibition for the test compounds (compared to dorzolamide result) are in the following order: Dorzolamide > **1h** > **1b** > **1f** > **1e** > **1k**. Other compounds (**1a** and **1r**) lacked significant CA II inhibitory activity in our assay (data not shown).

4. Conclusions

In conclusion, we have been able to introduce an efficient and environmentally friendly approach for the synthesis of *N*-acylsulfonamides via N-acylation of sulfonamides with carboxylic acid chlorides or anhydrides, using SSA as a solid acid catalyst in solvent-free and heterogeneous conditions. The reactions are characterized by non-corrosiveness, safety, low cost and waste, ease of separation, high yields, and chemoselectivity. Replacement of the liquid acids with a solid acid catalyst is a desirable feature of the reactions that may be important in their industrial manufacture. The solvent-free N-acylation has special advantages over the existing solvent added synthesis and is a green chemistry approach to the preparation of these compounds. Furthermore, microbiological activity of the test compounds was evaluated against a panel of resistant and susceptible Gram-positive and Gram-negative microorganisms in vitro comparable to that of sulfamethoxazole and also to some degree of CA II inhibitory activity. On the other

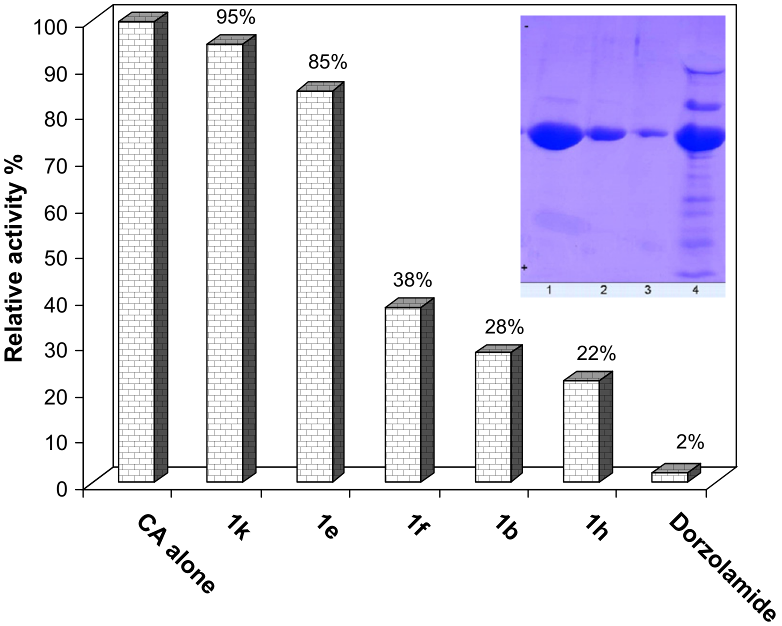


Figure 1. Inhibition of CA II activity by dorzolamide and synthesized test compounds. The reported results of CA II enzyme inhibition are averages of two separate experiments whenever the coefficients of variation were less than 5%. The final concentration of enzyme and CA/inhibitor molar ratio were 0.05 mg/mL and 1/15, respectively. Inset: the SDS–PAGE pattern of purified (lanes 1–3) and commercial (lane 4) carbonic anhydrase. Electrophoresis performed according to Laemmli on 10% slab gel.[35]

hand, we need to determine the mode (reversibility and/or irreversibility) of CA inhibition of the test compounds and also evaluate them quantitatively (determining of K_i and IC_{50} parameters), by comparing with reference inhibitors. Also, in our laboratory, further work is in process to design more potent and isoenzyme-specific CA inhibitors containing unsubstituted sulfonamide moiety.

5. Experimental

5.1. General methods

All chemicals were purchased from Merck and Fluka chemical companies. Infrared spectra were recorded on Nicollet (impact 400D model) FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 300 Avance spectrophotometer in DMSO-d_6 as the solvent and TMS as the internal standard. Column chromatography was performed using silica gel 60 (230–400 mesh). All yields refer to isolated products. Human CA II isoenzyme was purified according to Nyman's method with some minor modifications.[32] Protein concentration for carbonic anhydrase II was determined by absorbance at 280 nm with an extinction coefficient (ε_{280}) of 5.7×10^4 mol^{-1} cm^{-1}.[33]

5.2. Enzyme assay

The enzymatic activity of CA solution in the presence or absence of the enzyme inhibitor (reference drug and or test compounds) was determined based on *p*-nitrophenyl acetate esterase activity of the enzyme according to Pocker and co-workers.[34] The stock solution of the tested compounds and dorzolamide (1 mM) were dissolved in acetonitrile and distilled water, respectively. The CA inhibition potency of test compounds was determined by comparing the resulting initial rate with the initial rate of *p*-nitrophenyl acetate hydrolysis by the enzyme alone under all identical conditions.

5.3. Solvent-free synthesis of *N*-acylsulfonamides

To a vigorously stirred mixture of sulfonamide (1 mmol) and silica sulfuric acid (0.008 g) carboxylic acid chloride (2 mmol) or carboxylic acid anhydride (2 mmol) was added at room temperature. 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 filtrate was washed with water (15 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (60–120 mesh) using EtOAc–petroleum ether as eluent or recrystallized (toluene or ethyl acetate–*n*-hexane mixed solvent) to afford the corresponding *N*-acylsulfonamide in good to high yield.

5.4. Synthesis of *N*-acylsulfonamides in chloroform

A mixture of sulfonamide (1 mmol), carboxylic acid chloride (2 mmol), or carboxylic acid anhydride (2 mmol) was refluxed in chloroform (5 mL) in the presence of silica sulfuric acid (0.008 g) for an appropriate time (Table 1). The progress of the reaction was monitored by TLC. After the completion of the reaction, chloroform (20 mL) was added and the solid catalyst was removed by filtration. The filtrate was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified just like the above-mentioned procedure for the solvent-free condition. The structural assignments of the products are based on their IR, ^1H NMR, ^{13}C NMR or by comparison of their melting point with those of the known compounds.

5.4.1. *N*-Pentanoyl benzensulfonamide (1e). Mp 79–81 °C; IR υ (cm^{-1}) 3214, 1688, 1608, 1350, 1164; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm) 0.77 (t, $J = 7.2$ Hz, 3H), 1.13 (sextet, $J = 7.4$ Hz, 2H), 1.37 (quintet, $J = 7.4$ Hz, 2H), 2.19 (t, $J = 7.3$ Hz, 2H), 7.59–7.91 (m, 5H), 12.03 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 13.47, 21.31, 26, 34.97, 127.36, 129.04, 133.55, 139.38, 171.57.

5.4.2. *N*-Isobutanoyl-4-methyl benzensulfonamide (1j). Mp 111–113 °C; IR υ (cm^{-1}) 3259, 1731, 1329, 1171; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm) 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 (75 MHz, DMSO-d_6) δ (ppm) 16.92, 19.57, 32.75, 125.97, 128.03, 135.03, 142.61, 173.72.

5.4.3. *N*-Pentanoyl methansulfonamide (1q). Mp 69–71 °C; IR υ (cm^{-1}) 3269, 1720, 1330, 1158; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm) 0.86 (t, $J = 7.3$ Hz, 3H), 1.26 (sextet, $J = 7.4$ Hz, 2H), 1.48 (quintet, $J = 7.4$ Hz, 2H), 2.25 (t, $J = 7.3$ Hz, 2H), 3.2 (s, 3H), 11.62 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 14.06, 21.96, 26.62, 35.52, 43.55, 173.09.

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