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A novel and efficient solvent-free and heterogeneous method for the synthesis of primary, secondary and bis-*N*-acylsulfonamides using metal hydrogen sulfate catalysts

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ABSTRACT

Some metal hydrogen sulfates were used as acid catalysts in the N-acylation of different sulfonamides using carboxylic acid chlorides and anhydrides as acylating agents under both heterogeneous and solvent-free conditions. $Al(HSO_4)_3$ and $Zr(HSO_4)_4$ were found to have the highest activity and catalyze the reactions efficiently to furnish the primary *N*-acyl sulfonamides ($RCONHSO_2R'$), secondary *N*-acylsulfonamides ($RCONR''SO_2R'$) and bis-*N*-acylsulfonamnides [$RCO(SO_2R')N\text{-}R''\text{-}N(SO_2R')COR$] in good to high yield. The mild reaction conditions, inexpensive and low toxicity of catalysts and easy work-up procedure make this method attractive.

1. Introduction

N-Acylation of sulfonamides has attracted special attention in organic synthesis because of their pharmacological importance of the products.[1] This transformation is also a useful tool for lead optimization and lead generation.[2] *N*-Acylsulfonamides with their acidity make them suitable carboxylic acid proxies,[3] while their resistance to chemical and enzymatic hydrolysis renders them amenable for use as enzyme inhibitors.

Direct condensation of a carboxylic acid with a sulfonamide in the presence of coupling reagents, such as EDC·HCl[4] and DCC in the presence of DMAP[5] provides *N*-acylsulfonamides. Alternately, *N*-acylsulfonamide synthesis starts with the coupling of the parent sulfonamides with carboxylic acid chloride or anhydrides using trialkylamines, pyridine,[1a,6] or alkali hydroxides.[7] Formation of bis-acylated byproduct and difficult purification of *N*-acylsulfonamides are the main problems of these methods. There are a few reports mentioning this transformation under acidic condition. Corrosion caused by the liquid acid such as H_2SO_4 contamination of the waste water with acid, the high temperature needed to achieve conversion[8] and use of expensive or unavailable reagents are some of the limitations of these methods. Clearly, there is a need for development of a new, inexpensive and bench top acid that can promote the above reaction in a catalytic way.

There are significant demands by the pharmaceutical industries for new and efficient catalysts. Moreover, together with traditional criteria, such as good activity and selectivity; these new catalysts must include additional properties, such as low cost and environmental friendliness. In addition, there is current research and general interest in solvent-free[9] and heterogeneous[10] systems because of their importance in industry and in developing technologies. Between the huge numbers of reagents, solid acidic compounds, which are used as protic or Lewis acids, have special position in organic chemistry.[11] Among them, metal hydrogen sulfates have attracted the attention of organic chemist during the last decade.[12] In addition, the stability, low cost, heterogeneous nature of the reactions, high yields of the products, short reaction time, and reusability are among other important advantages of these reagents. Aluminum and zirconium hydrogen sulfates, as stable materials are efficient reagents which can be used for different functional group transformations.[13]

In continuation of our interest on sulfonamides and *N*-acylsulfonamides,[14] herein we report an attractive method using $Al(HSO_4)_3$ and $Zr(HSO_4)_4$ as catalysts for N-acylation of different sulfonamides with some carboxylic acid anhydride and chloride under solvent-free and heterogeneous conditions.

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2. Results and discussion

2.1. Catalysts characterization

The FTIR spectra of the $Al(HSO_4)_3$ and $Zr(HSO_4)_4$ catalysts is shown in Figure 1. As clearly seen in the Figure the intensity of the peak due to OH bending mode (probably due to M–OH groups) around 1620 cm^{-1} is low because of loading the support with H_2SO_4. Some additional peaks; asymmetric and symmetric stretching of S═O bond at 1229–1290 and 1177 cm^{-1}, respectively, confirm the presence of HSO_4 in the structure of the catalysts. The other peaks in the range of 750–1000 cm^{-1} may attributed to the S–O bond.

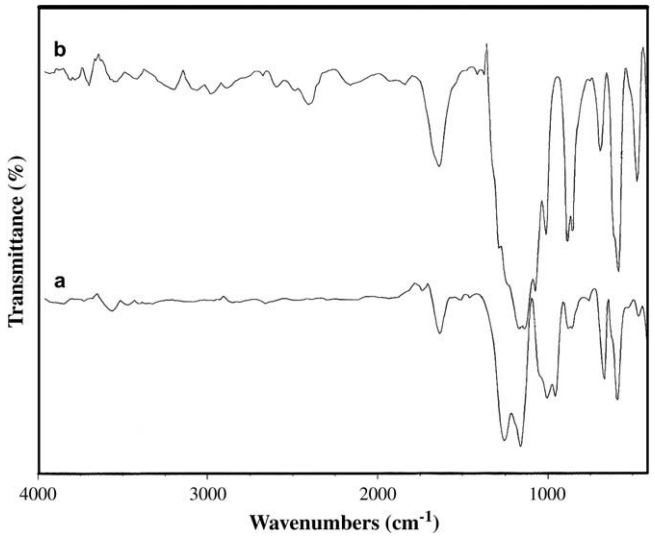


Figure 1. FTIR spectra of (a) $Zr(HSO_4)_4$; (b) $Al(HSO_4)_3$.

The nature of acid sites of the $Zr(HSO_4)_4$ and $Al(HSO_4)_3$ catalysts was determined by FTIR-pyridine adsorption study (Fig. 2) and the values are reported in Table 1. As it shown in Figure 2 $Zr(HSO_4)_4$ and $Al(HSO_4)_3$ have a broad acid sites distribution. Absorption bands around 1605, 1575, 1490 and 1444 cm^{-1} characteristic of Lewis acid sites[15] can be observed for the catalysts. Also Brønsted acidity (1540 cm^{-1} band) is observed in these catalysts and the concentration of Brønsted sites in the catalysts, especially in the $Al(HSO_4)_3$ catalyst is higher (Table 1).

Table 1
Absorbed and desorbed pyridine molecules on the $Al(HSO_4)_3$ and $Zr(HSO_4)_4$

Catalyst	Brønsted acidity (mmol kg^{-1}) (desorption temperature of pyridine)			Lewis acidity (mmol kg^{-1}) (desorption temperature of pyridine)		
	373 K	473 K	573 K	373 K	473 K	573 K
$Al(HSO_4)_3$	262.5	140.7	39.2	308	236.6	157.5
$Zr(HSO_4)_4$	218.4	175	175	287	280	250

According to the results of Figure 2 and Table 1, it can be seen that the acidity of $Al(HSO_4)_3$ catalyst is higher than the $Zr(HSO_4)_4$ catalyst. On the other hand, the acid sites in the $Zr(HSO_4)_4$ are more thermally stable and it's acidity is remaining even up to 573 K. The amount of Brønsted acidity of $Al(HSO_4)_3$ decreases about 85% with increase desorption temperature from 373 to 573 K. However, this is only about 20% for $Zr(HSO_4)_4$ catalyst.

The TG-DTG and DSC curves of the various samples have been investigated (Figs. 3 and 4). The $Zr(HSO_4)_4$ and $Al(HSO_4)_3$ sample shows three separate weight loss steps. The first, small (around 6%, w/w) step appearing at temperature <150 °C corresponds to the release of water (i.e., adsorbed water on the inner and outer surface). The second step (about 200–250 °C) can be attributed to the H_2SO_4 loss from the outer surface of the catalysts (around 10%, w/w). The third weight loss (about 250–300 °C) amounts around 45% (w/w) is related to the decomposition of the catalyst and production of SO_2. The DSC curve of these catalysts shows that the overall process is endothermic.

2.2. Optimization of the reaction conditions

In order to find the best reaction condition, the reaction was optimized with respect to the catalyst, solvent, temperature and reaction time. At first different metal hydrogen sulfates including; aluminum hydrogen sulfate, zirconium hydrogen sulfate, calcium hydrogen sulfate, cobalt hydrogen sulfate and magnesium hydrogen sulfate were screened for N-acylation of benzenesulfonamide and 4-methyl-*N*-propylbenzenesulfonamide with propionyl chloride and acetic anhydride to find the best catalyst. The results show that the reaction in the presence of $Al(HSO_4)_3$ and $Zr(HSO_4)_4$ (5 mol % for N-acylation of benzenesulfonamide and 10 mol % for N-acylation of 4-methyl-*N*-propylbenzenesulfonamide) furnished the expected *N*-acylsulfonamides in good to high yields (82–93%) in 5–15 min in CH_2Cl_2 and solvent-free condition. The reactions in the presence of

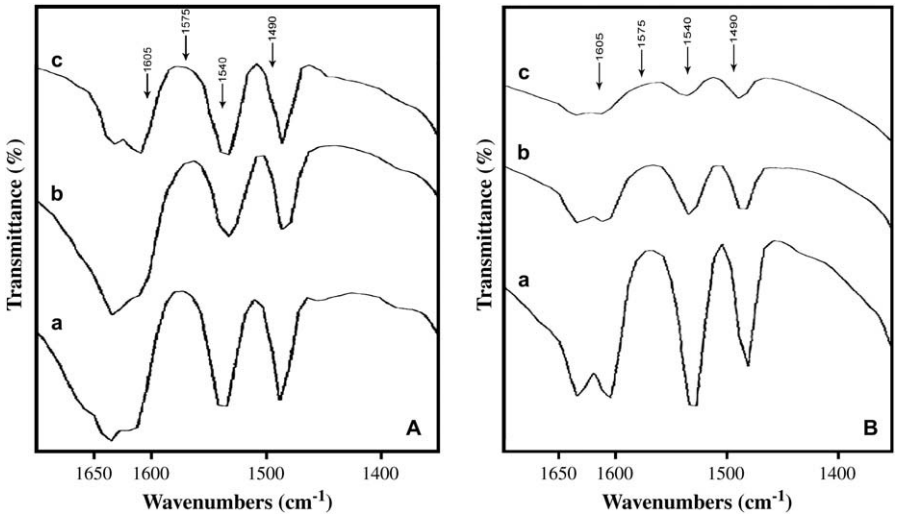


Figure 2. (A) FTIR spectra of: (a) pyridine desorption on $Zr(HSO_4)_4$ at 373 K; (b) pyridine desorption on $Zr(HSO_4)_4$ at 473 K; (c) pyridine desorption on $Zr(HSO_4)_4$ at 573 K. (B) FTIR spectra of: (a) pyridine desorption on $Al(HSO_4)_3$ at 373 K; (b) pyridine desorption on $Al(HSO_4)_3$ at 473 K; (c) pyridine desorption on $Al(HSO_4)_3$ at 573 K.

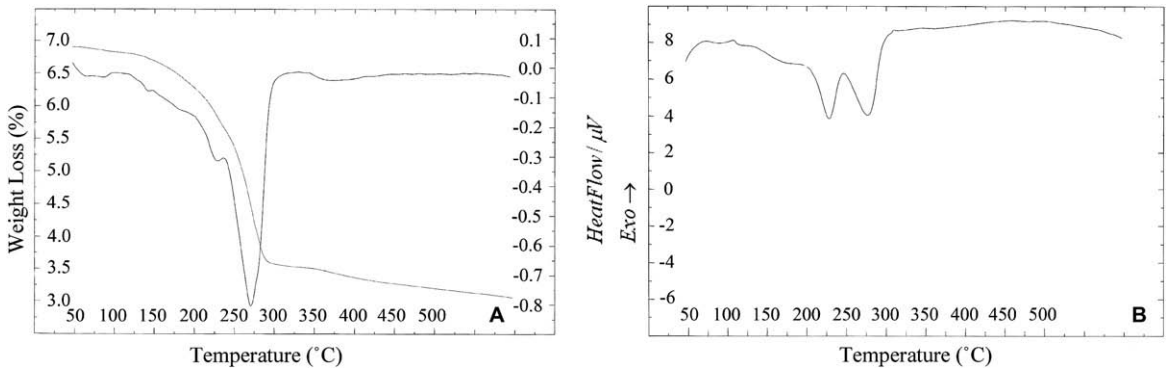


Figure 3. (A) TG-DTG curve of $Al(HSO_4)_3$, (B) DSC curve of $Al(HSO_4)_3$.

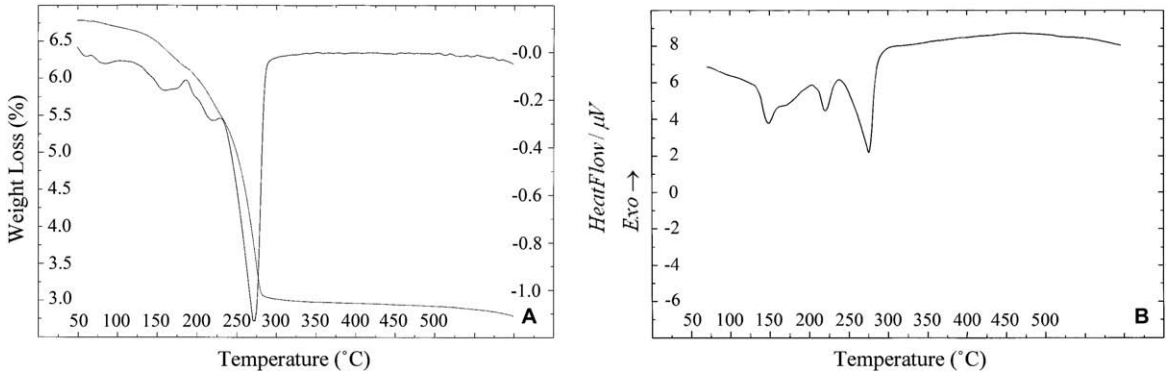
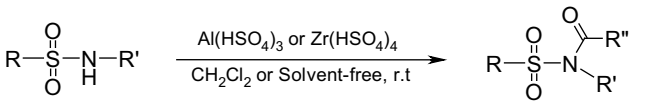


Figure 4. (A) TG-DTG curve of $Zr(HSO_4)_4$, (B) DSC curve of $Zr(HSO_4)_4$.

other catalysts required longer reaction time (25–45 min) and led to the products in lower yields (68–70%). Notably, no product was observed when the reaction was carried out in the absence of catalyst after 10 h. Therefore, $Al(HSO_4)_3$ and $Zr(HSO_4)_4$ were chosen for further study. To find the most suitable solvent, the reaction of benzenesulfonamide, 4-methyl-*N*-propylbenzenesulfonamide and bis-sulfonamide (**1g**) as examples of primary, secondary and bis-sulfonamides with propionyl chloride and acetic anhydride were carried out in different solvent such as CH_2Cl_2, $CHCl_3$, CH_3CN, THF, *n*-hexane and ethyl acetate. The best results were obtained when CH_2Cl_2 was used for N-acylation of primary and secondary sulfonamides at room temperature. In the case of bis-sulfonamide (**1g**), refluxing CH_3CN is the best condition for N-acylation reaction. The best reaction conditions were collected in Table 2.

2.3. N-Acylation of primary and secondary sulfonamides

It has been found that $Al(HSO_4)_3$ and $Zr(HSO_4)_4$ efficiently catalyzed the N-acylation of different primary and secondary sulfonamides under solvent-free and heterogeneous conditions at room temperature (Scheme 1). Methanesulfonamide, benzenesulfonamide

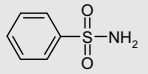
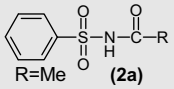
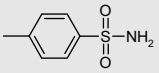
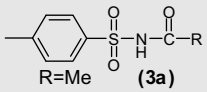
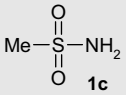
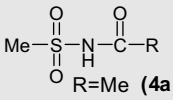


Scheme 1. N-Acylation of primary and secondary sulfonamides at room temperature.

Table 2
The best reaction conditions for the N-acylation of various sulfonamides

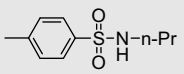
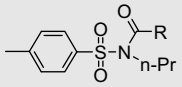
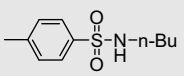
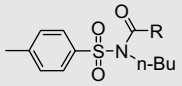
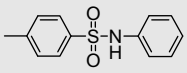
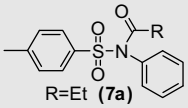
Entry	Sulfonamide	Acylating agent (mmol)	Catalyst (mmol)	Solvent	Temp (°C)	Time (min)	Yield (%)
1	$PhSO_2NH_2$ (**1a**)	C_2H_5COCl (1.1)	$Al(HSO_4)_3$ (0.05)	None	25	10	89
2	**1a**	$(C_2H_5CO)_2O$ (1.1)	$Al(HSO_4)_3$ (0.05)	None	25	5	88
3	**1a**	C_2H_5COCl (1.1)	$Al(HSO_4)_3$ (0.05)	CH_2Cl_2	25	8	80
4	**1a**	$(C_2H_5CO)_2O$ (1.1)	$Al(HSO_4)_3$ (0.05)	CH_2Cl_2	25	5	87
5	**1a**	C_2H_5COCl (1.3)	$Zr(HSO_4)_4$ (0.05)	None	25	20	88
6	**1a**	$(C_2H_5CO)_2O$ (1.3)	$Zr(HSO_4)_4$ (0.05)	None	25	5	85
7	**1a**	C_2H_5COCl (1.3)	$Zr(HSO_4)_4$ (0.05)	CH_2Cl_2	25	20	80
8	**1a**	$(C_2H_5CO)_2O$ (1.3)	$Zr(HSO_4)_4$ (0.05)	CH_2Cl_2	25	6	93
9	4-$MePhSO_2NHPr$ (**1d**)	C_2H_5COCl (1.5)	$Al(HSO_4)_3$ (0.1)	None	25	15	81
10	**1d**	$(C_2H_5CO)_2O$ (1.5)	$Al(HSO_4)_3$ (0.1)	None	25	2	90
11	**1d**	C_2H_5COCl (1.5)	$Al(HSO_4)_3$ (0.1)	CH_2Cl_2	25	15	88
12	**1d**	$(C_2H_5CO)_2O$ (1.5)	$Al(HSO_4)_3$ (0.1)	CH_2Cl_2	25	10	91
13	**1d**	C_2H_5COCl (1.5)	$Zr(HSO_4)_4$ (0.1)	None	25	20	83
14	**1d**	$(C_2H_5CO)_2O$ (1.5)	$Zr(HSO_4)_4$ (0.1)	None	25	15	81
15	**1d**	C_2H_5COCl (1.5)	$Zr(HSO_4)_4$ (0.1)	CH_2Cl_2	25	15	85
16	**1d**	$(C_2H_5CO)_2O$ (1.5)	$Zr(HSO_4)_4$ (0.1)	CH_2Cl_2	25	15	91
17	Bis-sulfonamide (**1g**)	$(C_2H_5CO)_2O$ (4.0)	$Al(HSO_4)_3$ (0.6)	CH_3CN	Reflux	8	92
18	**1g**	$(C_2H_5CO)_2O$ (4.0)	$Zr(HSO_4)_4$ (0.6)	CH_3CN	Reflux	10	88

Table 3
N-Acylation of primary sulfonamides using $Al(HSO_4)_3$ and $Zr(HSO_4)_4$ (5%) at room temperature

Entry	Sulfonamide	Acylating agent	Products	$Al(HSO_4)_3$		$Zr(HSO_4)_4$	
				Solvent free	CH_2Cl_2	Solvent free	CH_2Cl_2
				Time, min (yield, %)[a]	Time, min (yield, %)[a]	Time, min (yield, %)[a]	Time, min (yield, %)[a]
1	 **1a**	$(RCO)_2O$ R=Me	 R=Me **(2a)**	5(90)	7(91)	10(93)	15(90)
2	**1a**	R=*n*-Pr	R=*n*-Pr (**2b**)	5(87)	7(88)	10(90)	15(91)
3	**1a**	R=*i*-Pr	R=*i*-Pr (**2c**)	5(86)	7(85)	10(84)	15(81)
4	**1a**	R=Ph	R=Ph (**2d**)	20(75)	25(72)	60(78)	70(70)
5	**1a**	RCOCl R=Me	R=Me (**2a**)	10(87)	15(83)	20(80)	30(75)
6	**1a**	R=Et	R=Et (**2e**)	10(89)	15(83)	20(88)	30(80)
7	 **1b**	$(RCO)_2O$ R=Me	 R=Me **(3a)**	2(90)	5(86)	5(90)	7(90)
8	**1b**	R=Et	R=Et (**3b**)	2(92)	5(88)	5(89)	7(89)
9	**1b**	R=*n*-Pent	R=*n*-Pent (**3c**)	2(89)	5(89)	5(85)	7(85)
10	**1b**	R=*n*-Bu	R=*n*-Bu (**3d**)	2(91)	5(88)	5(90)	7(88)
11	**1b**	RCOCl R=Me	R=Me (**3a**)	10(86)	15(85)	20(85)	30(82)
12	 **1c**	$(RCO)_2O$ R=Me	 R=Me **(4a)**	2(88)	5(86)	5(96)	7(85)
13	**1c**	R=*i*-Pr	R=*i*-Pr (**4b**)	2(90)	5(89)	5(91)	7(85)
14	**1c**	R=*n*-Pent	R=*n*-Pent (**4c**)	2(90)	5(89)	5(87)	7(85)
15	**1c**	RCOCl R=Me	R=Me (**4a**)	10(95)	15(92)	20(87)	30(83)

[a] Yield refers to pure isolated products.

Table 4
N-Acylation of secondary sulfonamides using $Al(HSO_4)_3$ and $Zr(HSO_4)_4$ (10%) at room temperature

Entry	Sulfonamide	Acylating agent	Products	$Al(HSO_4)_3$		$Zr(HSO_4)_4$	
				Solvent free	CH_2Cl_2	Solvent free	CH_2Cl_2
				Time, min (yield, %)[a]	Time, min (yield, %)[a]	Time, min (yield, %)[a]	Time, min (yield, %)[a]
1	 **(1d)**	$(RCO)_2O$ R=Me	 R=Me **(5a)**	5(93)	7(90)	10(82)	15(80)
2	**1d**	R=*n*-Pr	R=*n*-Pr (**5b**)	5(95)	7(94)	10(80)	15(85)
3	**1d**	R=*n*-Bu	R=*n*-Bu (**5c**)	5(96)	7(93)	10(78)	15(82)
4	**1d**	R=*i*-Pr	R=*i*-Pr (**5d**)	5(85)	7(83)	10(71)	15(70)
5	**1d**	RCOCl R=Me	R=Me (**5a**)	10(87)	15(85)	15(85)	20(84)
6	 **(1e)**	$(RCO)_2O$ R=Me	 R = Me **(6a)**	5(90)	7(88)	10(82)	15(78)
7	**1e**	R=Et	R=Et (**6b**)	5(92)	7(89)	10(80)	15(81)
8	**1e**	R=*n*-Pr	R=*n*-Pr (**6c**)	5(92)	7(90)	10(78)	15(80)
9	**1e**	R=*n*-Bu	R=*n*-Bu (**6d**)	5(89)	7(85)	10(85)	15(82)
10	**1e**	RCOCl R=Et	R=Et (**6b**)	10(78)	15(80)	15(75)	20(75)
11	 **(1f)**	$(RCO)_2O$ R=Et	 R=Et **(7a)**	15(75)	20(75)	30(72)	45(72)
12	**1f**	R=*n*-Pr	R=*n*-Pr (**7b**)	15(75)	20(71)	30(70)	45(70)
13	**1f**	R=*n*-Bu	R=*n*-Bu (**7c**)	15(74)	20(70)	30(70)	45(70)
14	**1f**	R=*i*-Pr	R=*i*-Pr (**7d**)	15(72)	20(70)	30(71)	45(70)
15	**1f**	R=*n*-Pent	R=*n*-Pent (**7e**)	15(70)	20(70)	30(71)	45(70)
16	**1f**	RCOCl R=Me	R=Me (**7f**)	20(73)	30(70)	45(71)	60(70)

[a] Yield refers to pure isolated products.

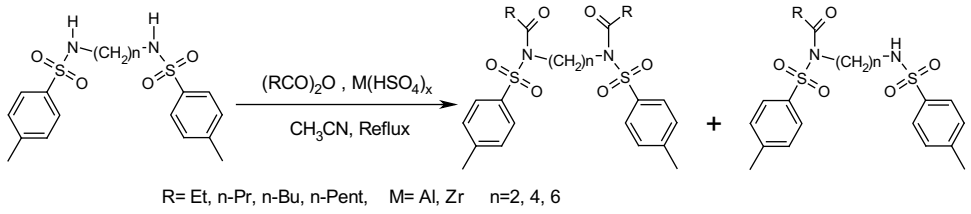
and 4-methylbenzenesulfonamide were used as primary sulfonamide. N-Acylation of secondary sulfonamide was tested with 4-methyl-*N*-propylbenzenesulfonamide, *N*-buthyl-4-methylbenzenesulfonamide and 4-methyl-*N*-phenylbenzenesulfonamide. Different carboxylic acid anhydrides, from acetic anhydride to *iso*-butanoic and hexanoic anhydride were used as acylating agent. Also, some carboxylic acid chlorides were examined as acylating agent, which we used recently for the first time as acylating agent in acidic condition.[10b] Several examples illustrating the usefulness of this efficient and rapid procedure are summarized in Tables 3 and 4. All of the substrates reacted smoothly to afford the corresponding *N*-acylsulfonamides in 70–96% yields in heterogeneous, solvent-free conditions. The aliphatic anhydride with long chain, like pentanoic and hexanoic anhydride (Table 3, entries 9, 14 and Table 4, entries 3, 9 and 15) could be used as effectively as one with short chain. Also, comparison between the results obtained in solution and those under solvent-free condition show that reaction proceeded faster in solvent-free condition.

Comparison between the results in Table 3 with Table 4 with respect to yields, reaction times and mol % of catalyst is interesting. In almost all cases, the reactions of primary sulfonamides in the presence of 5 mol % of catalysts were quicker than those of secondary sulfonamides in the presence of 5 mol % of catalysts and the products were obtained in higher yields. Probably, the most important factor is the steric hindrance. The bulky groups around the nitrogen (phenyl, propyl and butyl) decreases the nucleophilicity of secondary sulfonamides in compare to primary sulfonamides. Therefore, the reaction of secondary sulfonamides carried out in the presence of 10 mol % of catalysts. Also, N-acylation of *N*-alkylsulfonamides and *N*-arylsulfonamides are comparable. For example, reaction of *N*-butyl-4-methylbenzenesulfonamide (**1e**) with propionic anhydride after 5 min leads to the corresponding *N*-acylsulfonamide (**6b**) in 92% yield (Table 4, entry 7). On the other hand, it takes 15 min for the conversion 4-methyl-*N*-phenylbenzenesulfonamide (**1f**) to the (**7a**) in 75% yield (Table 4, entry 11). Perhaps, the difference is due to electron-withdrawing effect of phenyl group.

2.4. N-Acylation of bis-sulfonamides

In our knowledge, there are no previous examples of the synthesis of bis-*N*-acylsulfonamides, therefore, we sought to extend our preliminary observation to a range of these compounds. At first, several bis-sulfonamides were synthesized from sulfonylation of diamine including ethane-1,2-diamine, butane-1,4-diamine and hexane-1,6-diamine with benzenesulfonylchloride and 4-methylbenzenesulfonylchloride. The reactions were carried out in the presence of K_2CO_3 in solvent-free condition and the products were obtained in good to high yields after a simple work-up.[14a]

N-Acylation of bis-sulfonamides could be carried out using carboxylic acid anhydrides as acylating agent and $Al(HSO_4)_3$ and $Zr(HSO_4)_4$ as catalysts in refluxing CH_3CN. The mixtures of products formed during the reactions were mono-*N*-acylsulfonamides and bis-*N*-acylsulfonamides. (Scheme 2) It is expected that an increase in the concentration of acylating agent would increase the conversion of bis-sulfonamide to bis-*N*-acylsulfonamides. A series of experiments were performed to determine the effect of varying the ratio of reactants on this conversion. The mole ratios studies are within the range of 1–4 mol of butanoic anhydride based on 1 mol of bis-sulfonamide (**1g**). The results obtained are presented in Figure 5.



Scheme 2. N-Acylation of bis-sulfonamides in the presence of $Al(HSO_4)_3$ or $Zr(HSO_4)_4$.

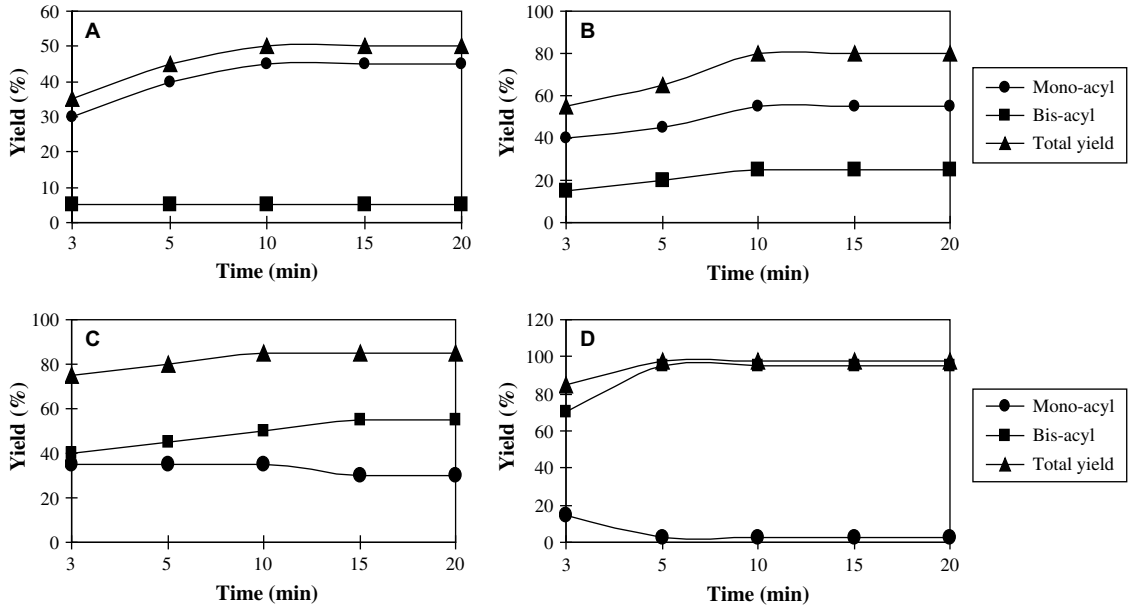


Figure 5. The effect of mole ratio of butanoic anhydride to bis-sulfonamide **1g** on the product composition A, 1:1, B, 2:1, C, 3:1, D, 4:1.

As it evident from the plots, the formation of bis-*N*-acylsulfonamide and also the overall conversion of bis-sulfonamide increase with increase in the mole ratio of acylating agent to sulfonamide up to a mole ratio 4:1. A further increase in the amount of anhydride causes a very low increase in the yield of products. The mole ratio of 4:1 of acylating agent to bis-sulfonamide is selected for further experimental studies due to its optimum performance. As shown in Table 5 by using these catalysts, various bis-sulfonamides were converted to their corresponding bis-*N*-acylsulfonamides in very good to excellent yields (88–94%) in very short reaction times (4–10 min). As the results shown, several structurally varied acylating agents underwent clean and remarkably fast N-acylation reaction. The acylation reaction with long chain carboxylic acid anhydride like hexanoic anhydride proceeded as fast as one with short chain (e.g., compare entry 1 with entry 3 in Table 5).

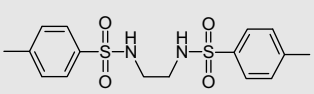
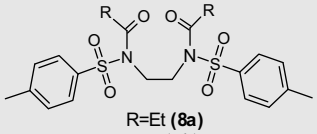
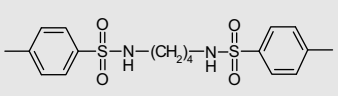
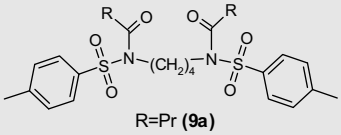
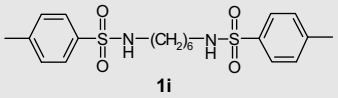
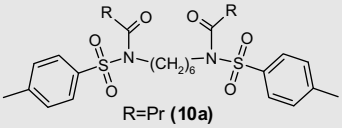
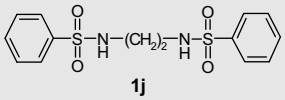
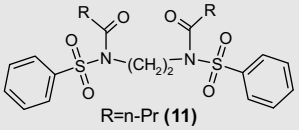
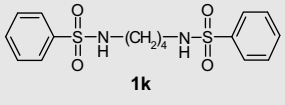
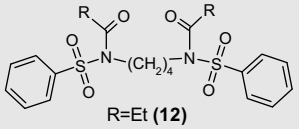
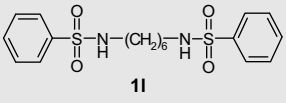
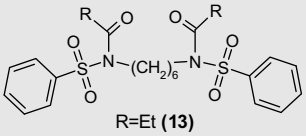
2.5. Catalyst reuse and stability

Finally, we were interested in studying the reusability of the catalysts due to economical and environmental aspects. For this purpose the reaction of 4-methyl-*N*-propylbenzenesulfonamide with pentanoic anhydride was chosen as a model reaction in the presence of $Al(HSO_4)_3$ and $Zr(HSO_4)_4$ in both heterogeneous and solvent-free conditions. At the end of each run, the catalysts were recovered from the reaction mixture by addition of ethyl acetate in the solvent-free and dichloromethane in heterogeneous reactions. Simple filtration and drying at 40 °C, was enough to purify the catalyst. The recycled $Al(HSO_4)_3$ was used for further runs and its activity did not shown any significant decrease even after five runs. The $Zr(HSO_4)_4$ was reused for three runs.

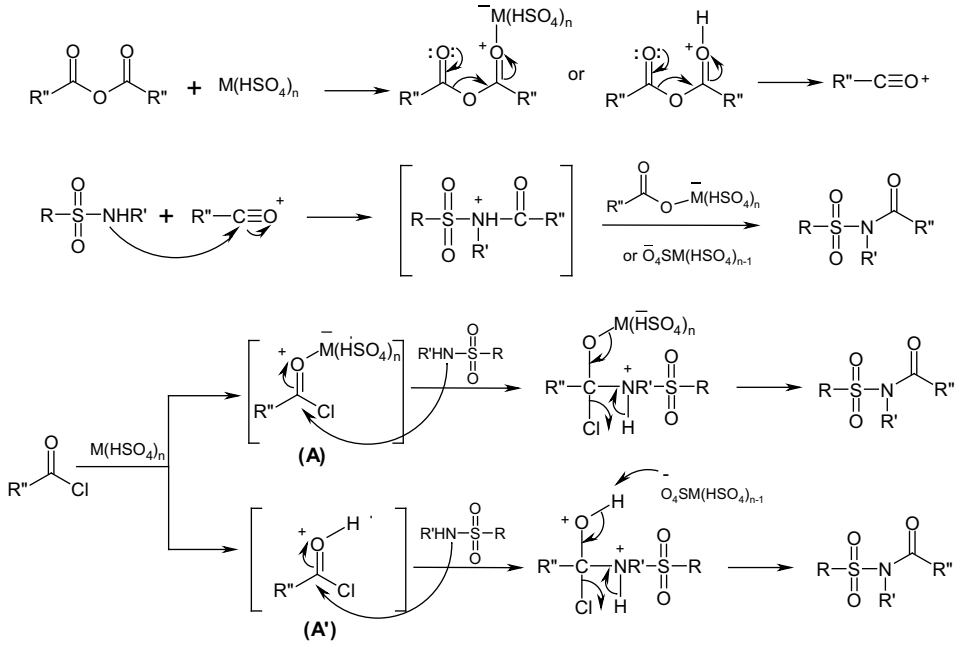
2.6. Mechanism

Although the precise mechanism of acid catalyst N-acylation of sulfonamides has not been elucidated yet, we suppose that the reaction happens by formation of reactive acylating intermediates. The results obtained during the N-acylation of sulfonamides with different acylating agents are in agreement with plausible mechanism for this reaction, which is depicted in Scheme 3. These results show that carboxylic acid anhydrides are slightly more reactive than

Table 5
N-Acylation of bis-sulfonamides with carboxylic acid anhydrides in refluxing CH_3CN

Entry	Sulfonamide	Acylating agent	Product	$Al(HSO_4)_3$ Time, min (yield, %)[a]	$Zr(HSO_4)_4$ Time, min (yield, %)[a]
1	 **1g**	$(RCO)_2O$ R=Et	 R=Et **(8a)**	8(92)	10(88)
2	**1g**	R=Pr	R=Pr (**8b**)	8(92)	10(90)
3	**1g**	R=*n*-Pent	R=*n*-Pent (**8c**)	6(92)	10(92)
4	 **1h**	$(RCO)_2O$ R=Pr	 R=Pr **(9a)**	5(90)	8(89)
5	**1h**	R=*n*-Bu	R=*n*-Bu (**9b**)	5(92)	8(90)
6	 **1i**	$(RCO)_2O$ R=Pr	 R=Pr **(10a)**	4(93)	8(88)
7	**1i**	R=*n*-Bu	R=*n*-Bu (**10b**)	4(95)	8(90)
8	 **1j**	$(RCO)_2O$ R=*n*-Pr	 R=n-Pr **(11)**	7(90)	10(90)
9	 **1k**	$(RCO)_2O$ R=Et	 R=Et **(12)**	6(92)	8(90)
10	 **1l**	$(RCO)_2O$ R=Et	 R=Et **(13)**	6(94)	8(92)

[a] Yield refers to pure isolated products.



Scheme 3. Plausible mechanism for metal hydrogen sulfate catalyze N-acylation of sulfonamide.

carboxylic acid chlorides (e.g., compare entries 7 with 10 in Table 4). Accordingly, metal hydrogen sulfate, catalyzing the reaction as acid, activated the carboxylic acid anhydride to form an acylinum ion. In the case of carboxylic acid chlorides, the intermediates **A** and **A′** were formed. Attack of the sulfonamide as nucleophile on acylinum ion or intermediates **A** and **A′**, leads to the *N*-acylsulfonamide and regeneration of catalyst. The acylinum ion is more reactive than the intermediates **A** and **A′** and therefore N-acylation of sulfonamides with carboxylic acid anhydride proceed faster than carboxylic acid chlorides. Also, this fact was supported further by the results of N-acylation of sulfonamides with electron withdrawing groups containing carboxylic acid anhydride. For example, the reaction of benzenesulfonamide with trifluoroacetic anhydride did not proceed considerably and only 10% of product was obtained after 10 h.

2.7. Spectral analysis

Spectral analysis of different synthesized *N*-acylsulfonamides supports the structure of the products. The IR spectra indicated the absence of N–H bond (except primary *N*-acylsulfonamide that appear as a sharp bond between 3100–3250 cm^{-1}) and exhibited the presence of sulfonyl (1150–1180 cm^{-1} and 1350–1380 cm^{-1}) and amide (1660–1700 cm^{-1}) groups. The ^1H NMR spectrum clearly showed the presence of 1,4-disubstituted benzene moieties. The presence of amide groups was further supported by the presence of carbonyl carbon resonance at 167–170 ppm in the ^{13}C NMR spectrum. Finally, the elemental analysis is in accordance with the proposed products.

3. Conclusion

$Al(HSO_4)_3$ and $Zr(HSO_4)_4$ have been proved to be effective catalysts for N-acylation of different sulfonamides affording the good to excellent yields of primary, secondary and bis-*N*-acylsulfonamides in solvent and solvent-free conditions. The catalysts are found to be mild and cheap with high catalytic activity, low toxicity, and moisture and air tolerance. This new strategy offer several advantages including simple and solvent-free experiment conditions, high yields, short reaction times and readily recyclable solid acid catalysts. It is believed that this method would be a useful synthetic methodology that is in agreement with green chemistry.

4. Experimental

4.1. Materials

All chemicals were purchased from Merck and Fluka chemical companies. Infrared spectra were recorded on Nicolet (impact 400D model) FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 300 Avance spectrophotometer in $CDCl_3$ as the solvent and TMS as internal standard. Column chromatography was performed using silica gel 60 (230–400 mesh). All yields refer to isolated yield. The catalysts were prepared according to Ref. 12b. Bis-sulfonamides were prepared according to Ref. 14a.

4.2. Characterization of the catalysts

Pyridine was used as a probe molecule to distinguish between Brønsted and Lewis acid sites.[16] Approximately 40–50 mg of material was pressed (for 3 min at 15 tones cm^{-2} pressure under approximately 10^{-2} Torr vacuum) into a self supporting wafer of 15 mm diameter. The wafer was treated with 26 mmHg of pyridine at 473 K for 1 h and evacuated at 373, 473 and 573 K for 1 h in dynamic vacuum. After each treatment, an IR spectrum was recorded at room temperature. The peak areas corresponding to the concentration of Brønsted and Lewis acid sites adsorbed pyridine were respectively collected at 1545 and 1445 cm^{-1}, using the extinction coefficients given by Emeis[17] (1.67 and 2.22 cm/μmol for Brønsted and Lewis acid sites respectively). The relevant peak areas calculated for all the catalysts are presented in Table 1.

Thermal gravimetric analysis (TGA) data for the organic compounds were obtained by a Mettler TGA-50 under air atmosphere at a rate of 10 °C/min.

4.3. General procedure for N-acylation of primary and secondary sulfonamides

(a) *Under solvent-free condition*. To a vigorously stirred mixture of finely powdered of sulfonamide (1 mmol) and $Al(HSO_4)_3$ or $Zr(HSO_4)_4$ (for primary sulfonamides 0.05 mmol and for secondary sulfonamide 0.1 mmol) in a 10 mL glass vessel, 1.1–1.5 mmol of

acylating agent (according to Table 1) was added at room temperature. After completion of the reaction (monitored by TLC), ethyl acetate (20 mL) was added and the catalyst was filtered off and washed with further solvent (5 mL). The filtrate was washed with water (15 mL) and was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by recrystallization from ethyl acetate/*n*-hexane mixed solvent or by column chromatography on silica gel (60–120 mesh, petroleum ether–ethyl acetate) to afford the corresponding *N*-acylsulfonamide in good to high yield.

(b) *In CH_2Cl_2*. To a stirred mixture of sulfonamide (1 mmol) and $Al(HSO_4)_3$ or $Zr(HSO_4)_4$ (for primary sulfonamides 0.05 mmol and for secondary sulfonamide 0.1 mmol) in 5 mL CH_2Cl_2, 1.1–1.5 mmol of acylating agent (according to Table 1) was added at room temperature. After completion of the reaction (monitored by TLC), the catalyst was filtered off and washed with CH_2Cl_2 (5 mL). The filtrate was washed with water (15 mL) and was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified as described above for solvent-free condition.

4.3.1. *N-Propyl-N-tosylacetamide (**5a**)*

Oil; R_f (33% ethyl acetate/hexane) 0.45; IR (KBr): 2966, 1706, 1464, 1355, 1262, 1167, 1090, 811 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.4 Hz, CH_2CH_3), 1.76 (2H, sext, *J* 7.4 Hz, CH_2CH_3), 2.31 (3H, s, CH_3Ph), 2.44 (3H, s, $COCH_3$), 3.74 (2H, t, *J* 7.4 Hz, NCH_2), 7.34 (2H, d, *J* 8.0 Hz, CH_3Ph *o*-H), 7.77 (2H, d, *J* 8.0 Hz, CH_3Ph *m*-H); δ_C (75 MHz, $CDCl_3$) 11.1, 21.6, 23.1, 24.9, 48.7, 127.4, 129.9, 136.8, 144.8, 170.1; (Found: C, 56.98; H, 6.91; N, 5.35. $C_{12}H_{17}NO_3S$ requires: C, 56.45; H, 6.71; N, 5.49%.)

4.3.2. *N-Butyl-N-tosylacetamide (**6a**)*

Oil; R_f (33% ethyl acetate/hexane) 0.50; IR (KBr): 2960, 2868, 1701, 1593, 1356, 1257, 1164, 1098, 959, 907, 814, 722, 662, 583 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.3 Hz, CH_2CH_3), 1.30 (2H, sext, *J* 7.3 Hz, CH_2CH_3), 1.63 (2H, quint, *J* 7.3 Hz, NCH_2CH_2), 2.24 (3H, s, CH_3Ph), 2.37 (3H, s, $COCH_3$), 3.73 (2H, t, *J* 7.3 Hz, NCH_2), 7.28 (2H, d, *J* 8.0 Hz, CH_3Ph *o*-H), 7.72 (2H, d, *J* 8.0 Hz, CH_3Ph *m*-H); δ_C (75 MHz, $CDCl_3$) 13.6, 20.0, 21.5, 24.8, 31.9, 46.9, 127.4, 129.8, 136.8, 144.8, 169.9; (Found: C, 58.38; H, 7.61; N, 5.35. $C_{13}H_{19}NO_3S$ requires: C, 57.97; H, 7.11; N, 5.20%.)

4.3.3. *N-Phenyl-N-tosylacetamide (**7f**)*

Mp: 153–155 °C [lit. 149–150 °C];[18] R_f (33% ethyl acetate/hexane) 0.40; IR (KBr): 2921, 1700, 1594, 1362, 1270, 1224, 1171, 1091, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.87 (3H, s, $COCH_3$), 2.47 (3H, s, CH_3Ph), 7.27–7.31 (2H, m, N*Ph* *m*-H), 7.35 (2H, d, *J* 8.0 Hz, CH_3Ph *o*-H), 7.48–7.52 (3H, m, N*Ph* *o*,*p*-H), 7.94 (2H, d, *J* 8.0 Hz, CH_3Ph *m*-H); δ_C (75 MHz, $CDCl_3$) 21.7, 25.1, 129.2, 129.4, 129.9, 130.0, 136.1, 136.9, 145.0, 170.1.

4.3.4. *N-Butyl-N-tosylpropionamide (**6b**)*

Mp: 75–77 °C; R_f (33% ethyl acetate/hexane) 0.45; IR (KBr): 2960, 2861, 1699, 1600, 1468, 1362, 1158, 992, 900, 814, 728, 669 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.3 Hz, $N(CH_2)_3CH_3$), 1.05 (3H, t, *J* 7.2 Hz, $COCH_2CH_3$), 1.36 (2H, sext, *J* 7.3 Hz, $N(CH_2)_2CH_2$), 1.70 (2H, quint, *J* 7.3 Hz, NCH_2CH_2), 2.43 (3H, s, CH_3Ph), 2.59 (2H, q, *J* 7.2 Hz, $COCH_2$), 3.79 (2H, t, *J* 7.3 Hz, NCH_2), 7.33 (2H, d, *J* 8.1 Hz, CH_3Ph *o*-H), 7.77 (2H, d, *J* 8.1 Hz, CH_3Ph *m*-H); δ_C (75 MHz, $CDCl_3$) 8.8, 13.7, 20.1, 21.6, 29.6, 32.1, 46.8, 127.5, 129.8, 137.0, 144.6, 173.7; (Found: C, 58.88; H, 7.61; N, 4.68. $C_{14}H_{21}NO_3S$ requires: C, 59.34; H, 7.47; N, 4.94%.)

4.3.5. *N-Phenyl-N-tosylpropionamide (**7a**)*

Mp: 142–145 °C [lit. 143–144 °C];[19] R_f (33% ethyl acetate/hexane) 0.44; IR (KBr): 2986, 2924, 1713, 1594, 1494, 1365, 1171, 1080, 964, 815 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.2 Hz, CH_2CH_3), 2.03 (2H, q, *J* 7.2 Hz, $COCH_2$), 2.46 (3H, s, CH_3Ph), 7.27–7.30 (2H, m, N*Ph* *m*-H), 7.35 (2H, d, *J* 8.1 Hz, CH_3Ph *o*-H), 7.49–7.51 (3H, m, N*Ph* *o*,*p*-H), 7.95 (2H, d, *J* 8.1 Hz, CH_3Ph *m*-H); δ_C (75 MHz, $CDCl_3$) 8.3, 21.7, 30.4, 129.2, 129.4, 129.9, 130.0, 130.0, 136.3, 136.4, 144.9, 173.6.

4.3.6. *N-Propyl-N-tosylbutyramide (**5b**)*

Oil; R_f (33% ethyl acetate/hexane) 0.45; IR (KBr): 2975, 2874, 1702, 1593, 1470, 1362, 1158, 1091, 808, 713, 669 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.83 (3H, t, *J* 7.3 Hz, $COCH_2CH_2CH_3$), 0.92 (3H, t, *J* 7.3 Hz, $N(CH_2)_2CH_3$), 1.56 (2H, sext, *J* 7.3 Hz, $COCH_2CH_2$), 1.72 (2H, sext, *J* 7.3 Hz, NCH_2CH_2), 2.41 (3H, s, CH_3Ph), 2.52 (2H, t, *J* 7.3 Hz, $COCH_2$), 3.74 (2H, t, *J* 7.3 Hz, NCH_2), 7.31 (2H, d, *J* 7.9 Hz, CH_3Ph *o*-H), 7.75 (2H, d, *J* 7.9 Hz, CH_3Ph *m*-H); δ_C (75 MHz, $CDCl_3$) 11.1, 13.5, 18.1, 21.6, 23.4, 38.0, 48.4, 127.5, 129.7, 137.1, 144.6, 172.9; (Found: C, 59.85; H, 7.11; N, 4.32. $C_{14}H_{21}NO_3S$ requires: C, 59.34; H, 7.47; N, 4.94%.)

4.3.7. *N-Butyl-N-tosylbutyramide (**6c**)*

Mp: 74–76 °C; R_f (33% ethyl acetate/hexane) 0.45; IR (KBr): 2960, 2868, 1706, 1468, 1356, 1257, 1164, 1098, 959, 907, 814, 722, 662, 583 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.84 (3H, t, *J* 7.3 Hz, $N(CH_2)_3CH_3$), 0.94 (3H, t, *J* 7.3 Hz, $CO(CH_2)_2CH_3$), 1.35 (2H, sext, *J* 7.3 Hz, $N(CH_2)_2CH_2$), 1.57 (2H, sext, *J* 7.3 Hz, $COCH_2CH_2$), 1.68 (2H, quint, *J* 7.3 Hz, NCH_2CH_2), 2.42 (3H, s, CH_3Ph), 2.54 (2H, t, *J* 7.3 Hz, $COCH_2$), 3.78 (2H, t, *J* 7.3 Hz, NCH_2), 7.32 (2H, d, *J* 8.1 Hz, CH_3Ph *o*-H), 7.76 (2H, d, *J* 8.1 Hz, CH_3Ph *m*-H); δ_C (75 MHz, $CDCl_3$) 13.5, 13.7, 18.1, 20.0, 21.6, 32.1, 38.0, 46.7, 127.5, 129.7, 137.1, 144.6, 172.9; (Found: C, 60.92; H, 7.29; N, 4.38. $C_{15}H_{23}NO_3S$ requires: C, 60.58; H, 7.79; N, 4.71%.)

4.3.8. *N-Phenyl-N-tosylbutyramide (**7b**)*

Mp: 112–115 °C; R_f (33% ethyl acetate/hexane) 0.53; IR (KBr): 2962, 2865, 1713, 1591, 1494, 1355, 1169, 1087, 944, 815, 705 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.77 (3H, t, *J* 7.3 Hz, CH_2CH_3), 1.51 (2H, sext, *J* 7.3 Hz, $CH_2CH_2CH_3$), 1.98 (2H, t, *J* 7.3 Hz, $COCH_2$), 2.46 (3H, s, CH_3Ph), 7.26–7.32 (2H, m, N*Ph* *m*-H), 7.34 (2H, d, *J* 8.0 Hz, CH_3Ph *o*-H), 7.48–7.53 (3H, m, N*Ph* *o*,*p*-H), 7.94 (2H, d, *J* 8.0 Hz, CH_3Ph *m*-H); δ_C (75 MHz, $CDCl_3$) 13.4, 17.7, 21.7, 38.5, 129.2, 129.4, 129.8, 129.9, 130.1, 136.3, 136.4, 144.8, 172.8; (Found: C, 64.72; H, 6.21; N, 4.78. $C_{17}H_{19}NO_3S$ requires: C, 64.33; H, 6.03; N, 4.41%.)

4.3.9. *N-Propyl-N-tosylpentanamide (**5c**)*

Oil; R_f (33% ethyl acetate/hexane) 0.45; IR (KBr): 2958, 2874, 1707, 1601, 1462, 1357, 1170, 1092, 986, 814 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.3 Hz, $CO(CH_2)_3CH_3$), 0.95 (3H, t, *J* 7.4 Hz, $N(CH_2)_2CH_3$), 1.26 (2H, sext, *J* 7.3 Hz, $CO(CH_2)_2CH_2$), 1.53 (2H, quint, *J* 7.3 Hz, $COCH_2CH_2$), 1.75 (2H, sext, *J* 7.4 Hz, NCH_2CH_2), 2.45 (3H, s, CH_3Ph), 2.57 (2H, t, *J* 7.3 Hz, $COCH_2$), 3.77 (2H, t, *J* 7.4 Hz, NCH_2), 7.34 (2H, d, *J* 8.1 Hz, CH_3Ph *o*-H), 7.78 (2H, d, *J* 8.1 Hz, CH_3Ph *m*-H); δ_C (75 MHz, $CDCl_3$) 11.2, 13.7, 21.6, 22.1, 23.4, 26.7, 35.9, 48.4, 127.5, 129.7, 137.1, 144.6, 173.1; (Found: C, 61.01; H, 7.42; N, 4.42. $C_{15}H_{23}NO_3S$ requires: C, 60.58; H, 7.79; N, 4.71%.)

4.3.10. *N-Butyl-N-tosylpentanamide (**6d**)*

Oil; R_f (33% ethyl acetate/hexane) 0.54; IR (KBr): 2960, 2868, 1706, 1600, 1468, 1358, 1257, 1164, 1091, 999, 913, 814, 722, 675, 590 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.75 (3H, t, *J* 7.3 Hz, $CO(CH_2)_3CH_3$), 0.86 (3H, t, *J* 7.3 Hz, $N(CH_2)_3CH_3$), 1.19 (2H, sext, *J* 7.3 Hz, $CO(CH_2)_2CH_2$), 1.31 (2H, sext, *J* 7.3 Hz, $N(CH_2)_2CH_2CH_3$), 1.45 (2H, quint, *J* 7.3 Hz, $COCH_2CH_2$), 1.62 (2H, quint, *J* 7.3 Hz, $NCH_2CH_2CH_2$), 2.34 (3H, s, CH_3Ph), 2.49 (2H, t, *J* 7.3 Hz, $COCH_2$), 3.73 (2H, t, *J* 7.3 Hz, NCH_2), 7.25 (2H, d, *J* 8.0 Hz, CH_3Ph *o*-H), 7.70 (2H, d, *J* 8.0 Hz, CH_3Ph *m*-H); δ_C (75 MHz, $CDCl_3$) 13.6, 13.7, 19.9, 21.4, 22.0, 26.6, 32.1, 35.8, 46.6, 127.4, 129.68, 137.1, 144.56, 172.9; (Found: C, 62.12; H, 7.69; N, 4.98. $C_{16}H_{25}NO_3S$ requires: C, 61.70; H, 8.09; N, 4.50%.)

*4.3.11. N-Phenyl-N-tosylpentanamide (**7c**)*

Mp: 84–87 °C; R_f (33% ethyl acetate/hexane) 0.53; IR (KBr): 2954, 1712, 1594, 1349, 1261, 1160, 877, 820, 707 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.76 (3H, t, *J* 7.3 Hz, CH_2CH_3), 1.15 (2H, sext, *J* 7.3 Hz, CH_2CH_3), 1.47 (2H, quint, *J* 7.3 Hz, $COCH_2CH_2$), 2.00 (2H, t, *J* 7.3 Hz, $COCH_2$), 2.46 (3H, s, CH_3Ph), 7.27–7.30 (2H, m, N*Ph m*-H), 7.35 (2H, d, *J* 8.1 Hz, CH_3*Ph o*-H), 7.49–7.51 (3H, m, N*Ph o*,*p*-H), 7.94 (2H, d, *J* 8.1 Hz, CH_3*Ph m*-H); δ_C (75 MHz, $CDCl_3$) 13.7, 21.7, 21.9, 26.3, 36.4, 129.2, 129.4, 129.8, 129.9, 130.1, 136.3, 136.4, 144.8, 172.7; (Found: C, 64.92; H, 6.21; N, 4.78. $C_{18}H_{21}NO_3S$ requires: C, 65.23; H, 6.39; N, 4.23%.)

*4.3.12. N-Propyl-N-tosylisobutyramide (**5d**)*

Oil; R_f (33% ethyl acetate/hexane) 0.50; IR (KBr): 2973, 2874, 1699, 1607, 1461, 1356, 1171, 1085, 992, 814, 715, 669, 583 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.4 Hz, CH_2CH_3), 0.97 (6H, d, *J* 6.6 Hz, $CH(CH_3)_2$), 1.69 (2H, sext, *J* 7.4 Hz, CH_2CH_3), 2.37 (3H, s, CH_3Ph), 3.11 (1H, sept, *J* 6.6 Hz, $CH(CH_3)_2$), 3.75 (2H, t, *J* 7.4 Hz, NCH_2), 7.28 (2H, d, *J* 8.0 Hz, CH_3*Ph o*-H), 7.72 (2H, d, *J* 8.0 Hz, CH_3*Ph m*-H); δ_C (75 MHz, $CDCl_3$) 11.1, 19.5, 21.5, 23.5, 33.9, 48.1, 127.3, 129.7, 137.2, 144.5, 177.8; (Found: C, 59.74; H, 7.1; N, 4.52. $C_{14}H_{21}NO_3S$ requires: C, 59.34; H, 7.47; N, 4.94%.)

*4.3.13. N-Phenyl-N-tosylisobutyramide (**7d**)*

Mp: 80–82 °C; R_f (33% ethyl acetate/hexane) 0.53; IR (KBr): 2969, 1704, 1599, 1494, 1363, 1263, 1164, 1098, 1028, 814, 706 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.98 (6H, d, *J* 6.7 Hz, $CH(CH_3)_2$), 2.30–2.36 (1H, m, $CH(CH_3)_2$), 2.46 (3H, s, CH_3Ph), 7.27–7.31 (2H, m, N*Ph m*-H), 7.34 (2H, d, *J* 8.1 Hz, CH_3*Ph o*-H), 7.50–7.51 (3H, m, N*Ph o*,*p*-H), 7.91 (2H, d, *J* 8.1 Hz, CH_3*Ph m*-H); (Found: C, 64.79; H, 6.31; N, 4.03. $C_{17}H_{19}NO_3S$ requires: C, 64.33; H, 6.03; N, 4.41%.)

*4.3.14. N-Phenyl-N-tosylhexanamide (**7e**)*

Mp: 100–102 °C; R_f (33% ethyl acetate/hexane) 0.50; IR (KBr): 2954, 1712, 1593, 1488, 1349, 1158, 1085, 814, 709, 576 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.79 (3H, t, *J* 7.4 Hz, CH_2CH_3), 1.08–1.20 (4H, m, $(CH_2)_2CH_3$), 1.48 (2H, quint, *J* 7.4 Hz, $COCH_2CH_2$), 1.99 (2H, t, *J* 7.4 Hz, $COCH_2$), 2.46 (3H, s, CH_3Ph), 7.28–7.29 (2H, m, N*Ph m*-H), 7.34 (2H, d, *J* 8.0 Hz, CH_3*Ph o*-H), 7.49–7.51 (3H, m, N*Ph o*,*p*-H), 7.94 (2H, d, *J* 8.0 Hz, CH_3*Ph m*-H); δ_C (75 MHz, $CDCl_3$) 13.8, 21.7, 22.3, 23.9, 30.9, 36.7, 129.2, 129.4, 129.8, 129.9, 130.1, 136.3, 136.4, 144.8, 173.0; (Found: C, 65.78; H, 6.31; N, 4.51. $C_{19}H_{23}NO_3S$ requires: C, 66.06; H, 6.71; N, 4.05%.)

4.4. General procedure for N-acylation of bis-sulfonamides in CH_3CN

A mixture of bis-sulfonamide (1 mmol) and carboxylic acid anhydride (4 mmol) was heated to reflux in CH_3CN (5 mL) in the presence of $Al(HSO_4)_3$ or $Zr(HSO_4)_4$ (0.2 g) for appropriate time according to Table 5. The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate (20 ml) was added and the catalyst was filtered off and washed with further solvent (5 mL). The filtrate was washed with water (15 ml) and was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (60–120 mesh, petroleum ether–ethyl acetate) to afford the corresponding bis-*N*-acylsulfonamide in good to high yield.

*4.4.1. Compound (**8a**)*

Mp: 169–170 °C; R_f (33% ethyl acetate/hexane) 0.40; IR (KBr): 2954, 1694, 1358, 1488, 1349, 1158, 1085, 814, 709, 576 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.10 (6H, t, *J* 7.2 Hz, CH_2CH_3), 2.45 (6H, s, CH_3Ph), 2.75 (4H, q, *J* 7.2 Hz, $COCH_2$), 4.05 (4H, s, NCH_2), 7.35 (4H, d, *J* 8.2 Hz, CH_3*Ph o*-H), 7.81 (4H, d, *J* 8.2 Hz, CH_3*Ph m*-H); δ_C (75 MHz, $CDCl_3$) 8.8, 21.7, 29.8, 45.2, 127.6, 129.9, 136.5, 145.0, 174.1; (Found: C, 54.34; H, 5.47; N, 5.94, $C_{22}H_{28}N_2O_6S_2$ requires: C, 54.98; H, 5.87; N, 5.83%.)

*4.4.2. Compound (**8b**)*

Mp: 126–127 °C; R_f (33% ethyl acetate/hexane) 0.43; IR (KBr): 2958, 1700, 1603, 1358, 1171, 1010, 864, 814, 745 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.90 (6H, t, *J* 7.3 Hz, CH_2CH_3), 1.64 (4H, sext, *J* 7.3 Hz, CH_2CH_3), 2.45 (6H, s, CH_3Ph), 2.71 (4H, t, *J* 7.3 Hz, $COCH_2$), 4.05 (4H, s, NCH_2), 7.35 (4H, d, *J* 8.1 Hz, CH_3*Ph o*-H), 7.81 (4H, d, *J* 8.1 Hz, CH_3*Ph m*-H); δ_C (75 MHz, $CDCl_3$) 13.6, 18.1, 21.6, 38.1, 45.2, 127.6, 129.9, 136.6, 144.9, 173.2; (Found: C, 55.98; H, 5.87; N, 5.83. $C_{24}H_{32}N_2O_6S_2$ requires: C, 56.67; H, 6.34; N, 5.51%.)

*4.4.3. Compound (**8c**)*

Mp: 123–124 °C; R_f (33% ethyl acetate/hexane) 0.40; IR (KBr): 2935, 1708, 1590, 1358, 1184, 1098, 810, 745 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.86 (6H, t, *J* 7.2 Hz, CH_2CH_3), 1.26 (8H, m, $(CH_2)_2CH_3$), 1.61 (4H, quint, *J* 7.2 Hz, $COCH_2CH_2$), 2.45 (6H, s, CH_3Ph), 2.70 (4H, t, *J* 7.2 Hz, $COCH_2$), 4.05 (4H, s, NCH_2), 7.35 (4H, d, *J* 8.2 Hz, CH_3*Ph o*-H), 7.81 (4H, d, *J* 8.2 Hz, CH_3*Ph m*-H); δ_C (75 MHz, $CDCl_3$) 13.9, 21.6, 22.4, 24.3, 31.1, 36.2, 45.3, 127.6, 129.9, 136.5, 144.9, 173.4; (Found: C, 59.98; H, 7.87; N, 5.33. $C_{28}H_{40}N_2O_6S_2$ requires: C, 59.55; H, 7.14; N, 4.96%.)

*4.4.4. Compound (**9a**)*

Mp: 126–127 °C; R_f (33% ethyl acetate/hexane) 0.53; IR (KBr): 2965, 1706, 1603, 1358, 1171, 1055, 1010, 881, 822, 687 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.86 (6H, t, *J* 7.30 Hz, CH_2CH_3), 1.59 (4H, sext, *J* 7.3 Hz, CH_2CH_3), 1.77 (4H, m, NCH_2CH_2), 2.45 (6H, s, CH_3Ph), 2.58 (4H, t, *J* 7.3 Hz, $COCH_2$), 3.83 (4H, m, NCH_2), 7.35 (4H, d, *J* 8.1 Hz, CH_3*Ph o*-H), 7.78 (4H, d, *J* 8.1 Hz, CH_3*Ph m*-H); δ_C (75 MHz, $CDCl_3$) 13.5, 18.1, 21.6, 27.2, 38.1, 46.2, 127.4, 129.9, 136.96, 144.8, 172.9; (Found: C, 58.98; H, 5.67; N, 5.83. $C_{26}H_{36}N_2O_6S_2$ requires: C, 58.19; H, 6.76; N, 5.22%.)

*4.4.5. Compound (**9b**)*

Mp: 143–144 °C; R_f (33% ethyl acetate/hexane) 0.50; IR (KBr): 2958, 1700, 1603, 1475, 1358, 1171, 1010, 688, 745 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.85 (6H, t, *J* 7.3 Hz, CH_2CH_3), 1.27 (4H, sext, *J* 7.3 Hz, CH_2CH_3), 1.54 (4H, quint, *J* 7.3 Hz, $COCH_2CH_2$), 1.77 (4H, m, NCH_2CH_2), 2.45 (6H, s, CH_3Ph), 2.59 (4H, t, *J* 7.3 Hz, $COCH_2$), 3.84 (4H, m, NCH_2), 7.35 (4H, d, *J* 8.2 Hz, CH_3*Ph o*-H), 7.78 (4H, d, *J* 8.2 Hz, CH_3*Ph m*-H); δ_C (75 MHz, $CDCl_3$) 13.8, 21.6, 22.1, 26.7, 27.2, 26.0, 46.2, 127.4, 129.9, 137.0, 144.8, 173.1; (Found: C, 60.08; H, 7.76; N, 5.38. $C_{28}H_{40}N_2O_6S_2$ requires: C, 59.55; H, 7.14; N, 4.96%.)

*4.4.6. Compound (**10a**)*

Mp: 111–113 °C; R_f (33% ethyl acetate/hexane) 0.40; IR (KBr): 2926, 1713, 1597, 1358, 1171, 1087, 829, 726 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.87 (6H, t, *J* 7.3 Hz, CH_2CH_3), 1.39 (4H, m, $N(CH_2)_2CH_2$), 1.60 (4H, sext, *J* 7.3 Hz, CH_2CH_3), 1.73 (4H, m, NCH_2CH_2), 2.45 (6H, s, CH_3Ph), 2.57 (4H, t, *J* 7.3 Hz, $COCH_2$), 3.79 (4H, t, *J* 7.7 Hz, NCH_2), 7.35 (4H, d, *J* 8.2 Hz, CH_3*Ph o*-H), 7.78 (4H, d, *J* 8.2 Hz, CH_3*Ph m*-H); δ_C (75 MHz, $CDCl_3$) 13.5, 18.1, 21.6, 26.3, 29.8, 38.1, 46.7, 127.5, 129.8, 137.1, 144.6, 172.9; (Found: C, 59.08; H, 7.43; N, 4.80. $C_{28}H_{40}N_2O_6S_2$ requires: C, 59.55; H, 7.14; N, 4.96%.)

*4.4.7. Compound (**10b**)*

Mp: 116–117 °C; R_f (33% ethyl acetate/hexane) 0.44; IR (KBr): 2958, 1706, 1597, 1364, 1171, 1029, 843, 729 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.85 (6H, t, *J* 7.3 Hz, CH_2CH_3), 1.27 (4H, sext, *J* 7.3 Hz, CH_2CH_3), 1.39 (4H, m, $N(CH_2)_2CH_2$), 1.54 (4H, quint, *J* 7.3 Hz, $COCH_2CH_2$), 1.73 (4H, m, NCH_2CH_2), 2.45 (6H, s, CH_3Ph), 2.58 (4H, t, *J* 7.3 Hz, $COCH_2$), 3.79 (4H, t, *J* 7.7 Hz, NCH_2), 7.34 (4H, d, *J* 8.1 Hz, CH_3*Ph o*-H), 7.78 (4H, d, *J* 8.1 Hz, CH_3*Ph m*-H); δ_C (75 MHz, $CDCl_3$) 13.8, 21.6, 22.1, 26.3, 26.7, 29.8, 36.0, 46.8, 127.5, 129.8, 137.1, 144.7, 173.1; (Found: C, 60.28; H, 7.76; N, 5.18. $C_{30}H_{44}N_2O_6S_2$ requires: C, 60.78; H, 7.48; N, 4.73%.)

*4.4.8. Compound (**11**)*

Mp: 115–116 °C; R_f (33% ethyl acetate/hexane) 0.43; IR (KBr): 2965, 1713, 1603, 1475, 1352, 1177, 1093, 881, 745 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.90 (6H, t, *J* 7.3 Hz, CH_2CH_3), 1.63 (4H, sext, *J* 7.3 Hz, CH_2CH_3), 2.71 (4H, t, *J* 7.3 Hz, $COCH_2$), 4.05 (4H, s, NCH_2), 7.54–7.94 (10H, m, Ph); δ_C (75 MHz, $CDCl_3$) 13.5, 18.1, 38.2, 45.3, 127.5, 129.3, 133.8, 139.5, 173.3; (Found: C, 55.34; H, 6.51; N, 6.04, $C_{22}H_{28}N_2O_6S_2$ requires: C, 54.98; H, 5.87; N, 5.83%.)

*4.4.9. Compound (**12**)*

Mp: 154–155 °C; R_f (33% ethyl acetate/hexane) 0.40; IR (KBr): 2926, 1455, 1352, 1177, 1085, 816, 758 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.07 (6H, t, *J* 7.2 Hz, CH_2CH_3), 1.79 (4H, m, NCH_2CH_2), 2.63 (4H, q, *J* 7.2 Hz, $COCH_2$), 3.86 (4H, s, NCH_2), 7.54–7.92 (10H, m, Ph); δ_C (75 MHz, $CDCl_3$) 8.8, 27.2, 29.8, 46.3, 127.4, 129.3, 133.7, 139.8, 173.7; (Found: C, 55.50; H, 6.31; N, 6.14. $C_{22}H_{28}N_2O_6S_2$ requires: C, 54.98; H, 5.87; N, 5.83%.)

*4.4.10. Compound (**13**)*

Mp: 135–136 °C; R_f (33% ethyl acetate/hexane) 0.40; IR (KBr): 2945, 1694, 1358, 1171, 1048, 861, 739 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.07 (6H, t, *J* 7.2 Hz, CH_2CH_3), 1.40 (4H, m, $N(CH_2)_2CH_2$), 1.75 (4H, m, NCH_2CH_2), 2.62 (4H, q, *J* 7.2 Hz, $COCH_2$), 3.81 (4H, t, *J* 7.2 Hz, NCH_2), 7.54–7.92 (10H, m, Ph); δ_C (75 MHz, $CDCl_3$) 8.8, 26.2, 29.7, 29.8, 46.9, 127.5, 129.2, 133.6, 139.9, 173.7; (Found: C, 56.08; H, 5.93; N, 5.09. $C_{24}H_{32}N_2O_6S_2$ requires: C, 56.67; H, 6.34; N, 5.51%.)

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