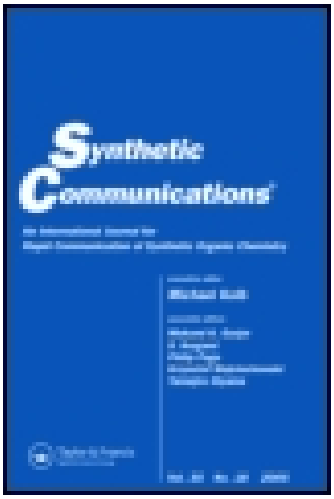


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis, Characterization, and Antimicrobial Evaluation of Sulfonamides Containing N-Acyl Moieties Catalyzed by Bismuth(III) Salts Under Both Solvent and Solvent-Free Conditions

Hadi Adibi [a], Ahmad Reza Massah [b], Mohammad Bagher Majnooni [a], Sherita Shahidi [b], Maryam Afshar [b], Ramin Abiri [c] & Hamid Javaherian Naghash [b]

[a] Department of Medicinal Chemistry, Faculty of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Islamic Republic of Iran

[b] Department of Chemistry, Islamic Azad University, Shahreza Branch, Shahreza, Islamic Republic of Iran

[c] Department of Microbiology, Faculty of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Islamic Republic of Iran

Published online: 09 Aug 2010.

To cite this article: Hadi Adibi, Ahmad Reza Massah, Mohammad Bagher Majnooni, Sherita Shahidi, Maryam Afshar, Ramin Abiri & Hamid Javaherian Naghash (2010) Synthesis, Characterization, and Antimicrobial Evaluation of Sulfonamides Containing N-Acyl Moieties Catalyzed by Bismuth(III) Salts Under Both Solvent and Solvent-Free Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:18, 2753-2766, DOI: 10.1080/00397910903318732

To link to this article: http://dx.doi.org/10.1080/00397910903318732

Synthetic Communications®, 40: 2753–2766, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903318732

Taylor & Francis
Taylor & Francis Group

SYNTHESIS, CHARACTERIZATION, AND ANTIMICROBIAL EVALUATION OF SULFONAMIDES CONTAINING *N*-ACYL MOIETIES CATALYZED BY BISMUTH(III) SALTS UNDER BOTH SOLVENT AND SOLVENT-FREE CONDITIONS

Hadi Adibi,[1] Ahmad Reza Massah,[2] Mohammad Bagher Majnooni,[1] Sherita Shahidi,[2] Maryam Afshar,[2] Ramin Abiri,[3] and Hamid Javaherian Naghash[2]

[1]*Department of Medicinal Chemistry, Faculty of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Islamic Republic of Iran*
[2]*Department of Chemistry, Islamic Azad University, Shahreza Branch, Shahreza, Islamic Republic of Iran*
[3]*Department of Microbiology, Faculty of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Islamic Republic of Iran*

Efficient N-acylation of sulfonamides with both readily available carboxylic acid chlorides and anhydrides has been carried out with catalysis by bismuth(III) salts including $BiCl_3$ and Bi $(OTf)_3$. The reactions proceed rapidly in both heterogeneous and solvent-free conditions and afforded the corresponding N-acylsulfonamides in good to excellent yields. The mild reaction conditions and low toxicity of bismuth salts make this procedure attractive and in close agreement with the goals of green chemistry. Some of the synthesized compounds were evaluated in vitro as antimicrobial agents against representative strains of Gram-positive (*Staphylococcus aureus *ATCC 25922, clinical strains of* Staphylococcus aureus *VISA and* Enterococcus *spp.) and Gram-negative bacteria (*Pseudomonas aeruginosa *ATCC 27853, clinical strains of* Klebsiella pneumonia *and* Escherichia coli*) and as antifungal agents against* Candida albicans *(clinically isolated) by both disc diffusion and minimal inhibition concentration (MIC) methods. All these bacteria and fungi studied were screened against some antibiotics to compare with our chemicals' zone diameters.

Keywords: Antimicrobial activity; bismuth(iii) salts; N-acylation; *N*-acylsulfonamide; solvent-free

INTRODUCTION

Sulfonamides are among the most widely used antibacterial agents in the world, chiefly because of their low cost, low toxicity, and excellent activity against common bacterial diseases.[1] The synergetic action of sulfonamides with trimethoprim has

Received August 8, 2009.

Address correspondence to Hadi Adibi, Department of Medicinal Chemistry, Faculty of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah 67145-1673, Islamic Republic of Iran, and Ahmad Reza Massah, Department of Chemistry, Islamic Azad University, Shahreza Branch, Shahreza 86145-311, Islamic Republic of Iran. E-mail: hadibi@kums.ac.ir; massah@iaush.ac.ir

brought about enormous resurgence of sulfonamide usage everywhere over the past decade. *N*-Acylsulfonamides have received considerable attention because of their diverse biological activities as precursors of therapeutic agents for Alzheimer's disease,[2] antibacterial inhibitors of tRNA synthetases,[3] prostaglandin F1a sulfonamides for the potential treatments of osteoporosis,[4] antagonists for angiotensin II,[5] and leukotriene D4-receptors.[6]

The most common methods for N-acylation of sulfonamides with different acylating agents have utilized suitable bases such as pyridine,[7,8] 4-*N,N*-dimethyl pyridine,[9,10] and alkali hydroxides.[11–13] Formation of bis-acylated by-products is the most important restriction of these methods. Recently, the first solvent-free procedure for the N-acylation of sulfonamides in the presence of potassium carbonates has been performed that overcomes the restriction of the other methods.[14] On the other hand, there are a few reports mentioning this transformation under acidic conditions. Some of the methods reported include acylation of sulfonamides with concentrated H_2SO_4 in the carboxylic acid anhydride as solvent[15] or in acetonitrile[16] and also using Fe-exchanged montmorillonite K10.[17] Very recently, we have demonstrated the applicability of protic solid acids such as silica chloride[18] and silica phosphoric acid[19] for N-acylation of sulfonamides. Unfortunately, many of these methods have drawbacks such as long reaction times, vigorous reaction conditions, use of expensive or unavailable reagents, poor yields of products, and tedious workups. Furthermore, most of these methods occur in solvent media, contrary to green chemistry. Clearly, there is a need for development of a new, inexpensive, benchtop acid that can promote this reaction in a catalytic way.

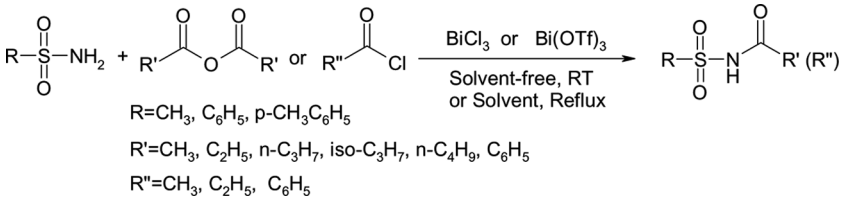
Bismuth compounds have recently received a lot of attention because of their low toxicity, low cost, and good stability.[20–23] Bismuth(III) salts have been reported as catalyst for epoxide opening,[24] Mannich-type reactions,[25] Mukaiyama-aldol reactions,[26] Claisen rearrangement,[27] deprotection of 1,1-diacetates,[28] and acetylation and benzoylation of alcohols and phenols.[29] $Bi(OTf)_3$ and $BiCl_3$ are particularly attractive because they are commercially available or can be easily prepared from commercially available starting materials. In continuation of our studies in this regard,[30] we decided to apply these reagents to the N-acylation of sulfonamides and evaluate their antimicrobial activity.

RESULTS AND DISCUSSION

Chemistry

An efficient method is reported here using $Bi(OTf)_3$ and $BiCl_3$ as catalysts for N-acylation of different sulfonamides with some carboxylic acid anhydride and chloride in solvent-free and heterogeneous conditions (Scheme 1). In a simple procedure, a mixture of reactants was vigorously stirred at room temperature in solvent-free condition or refluxed in suitable solvents for the appropriate times. The progress of the reactions was monitored by thin-layer chromatography (TLC), and the products were isolated in good to excellent yields (82–98%) in an easy workup procedure.

At first, the reaction was optimized with respect to the solvent, amount of catalyst, temperature, and reaction time. To find the best solvent, the reaction of



Scheme 1. $BiCl_3$- and $Bi(OTf)_3$-catalyzed N-acylation of sulfonamides.

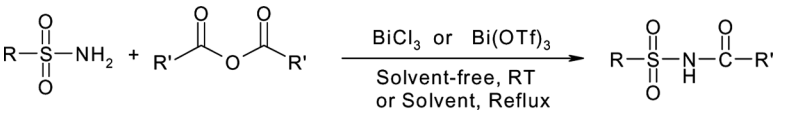
benzenesulfonamide with acetic anhydride was carried out in different solvents. Even though the reactions in $CHCl_3$ and CH_2Cl_2 led to a small amount of side products, an excellent yield was obtained, and these were selected as solvents for further studies. Also, the N-acylation of benzenesulfonamide was tried with varying amounts of catalyst in solvent and solvent-free conditions. We attempted the reaction of benzenesulfonamide with 2 equivalents acetic anhydride or acetyl chloride in the presence of 5 mol% of $Bi(OTf)_3$ at room temperature or in refluxed CH_2Cl_2. The reactions were completed within 1–5 min, and the pure *N*-acetylsulfonamide was obtained in 91–94% yield by just passing through a small silica-gel column. In a similar manner, benzenesulfonamide was also converted to *N*-acetylsulfonamide using 10 mol% of $BiCl_3$ within 13–17 min. By reducing the amount of acylating agents or catalysts, there were a considerable change in reaction time and yield in both solvent and solvent-free conditions. To evaluate the role of catalysts, we tried the N-acylation of benzenesulfonamide with acetic anhydride and acetyl chloride in the absence of $Bi(OTf)_3$ or $BiCl_3$. The reaction did not occur after 48 h. The best conditions for the N-acylation of benzenesulfonamide are summarized in Table 1.

The $BiCl_3$- and $Bi(OTf)_3$-catalyzed N-acylation reactions were applied to a range of sulfonamides, carboxylic acid anhydrides, and carboxylic acid chlorides (Tables 2 and 3). The reaction proceeded very efficiently in all cases. As shown in Table 2, benzenesulfonamide, 4-methyl benzenesulfonamide, and methanesulfonamide underwent clean and remarkably fast N-acylation reaction with several aliphatic and aromatic carboxylic acid anhydrides. The aliphatic carboxylic acid anhydrides with long chains, like pentanoic anhydride (Table 2, entries 4, 10, and 16) and also the relatively bulky isobutanoic anhydride (Table 2, entries 5, 11, and 17), were converted to the corresponding *N*-acylsulfonamides in excellent yields in

Table 1. Best reaction conditions in the N-acylation of benzenesulfonamide

Entry	Conditions	Yield (%)
1	$Bi(OTf)_3$ 5%/Solvent-free/25°C/Acetyl chloride/3 min	92
2	$Bi(OTf)_3$ 5%/Solvent-free/25°C/Acetic anhydride/1 min	92
3	$Bi(OTf)_3$ 5%/CH_2Cl_2/Reflux/Acetyl chloride/5 min	91
4	$Bi(OTf)_3$ 5%/CH_2Cl_2/Reflux/Acetic anhydride/2 min	94
5	$BiCl_3$ 10%/Solvent-free/25°C/Acetyl chloride/16 min	88
6	$BiCl_3$ 10%/Solvent-free/25°C/Acetic anhydride/13 min	91
7	$BiCl_3$ 10%/$CHCl_3$/Reflux/Acetyl chloride/17 min	87
8	$BiCl_3$ 10%/$CHCl_3$/Reflux/Acetic anhydride/15 min	90

Table 2. N-Acylation of sulfonamides with carboxylic acid anhydride in solvent or solvent-free conditions

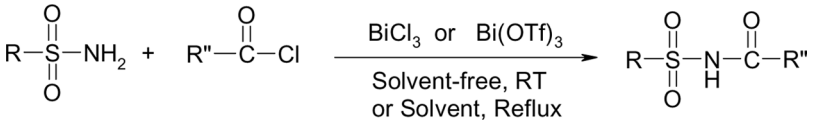


			Catalyst: $Bi(OTf)_3$ (5%)				Catalyst: $BiCl_3$ (10%)			
			Solvent-free		CH_2Cl_2		Solvent-free		$CHCl_3$	
Entry	R	R′	Time[a]	Yield[b]	Time[a]	Yield[b]	Time[a]	Yield[b]	Time[a]	Yield[b]
1	CH_3	CH_3	1	90	2	90	10	88	10	90
2	CH_3	C_2H_5	1	90	2	91	10	85	12	88
3	CH_3	C_3H_7	1	90	1	91	8	85	10	88
4	CH_3	C_4H_9	1	91	5	90	10	88	13	90
5	CH_3	$CH(CH_3)_2$	1	90	2	91	10	90	13	91
6	CH_3	Ph	15	90	30	91	60	82	60	87
7	CH_3-Ph	CH_3	2	90	2	94	15	89	20	90
8	CH_3-Ph	C_2H_5	3	91	2	93	17	90	20	92
9	CH_3-Ph	C_3H_7	3	91	3	90	20	88	20	90
10	CH_3-Ph	C_4H_9	3	92	3	96	22	90	20	88
11	CH_3-Ph	$CH(CH_3)_2$	1	92	1	91	17	88	20	89
12	CH_3-Ph	Ph	50	90	30	88	70	80	80	82
13	Ph	CH_3	1	92	2	94	13	91	15	90
14	Ph	C_2H_5	2	93	2	92	17	90	17	89
15	Ph	C_3H_7	3	90	2	95	12	85	17	90
16	Ph	C_4H_9	3	94	3	92	16	86	20	90
17	Ph	$CH(CH_3)_2$	1	94	1	96	15	88	20	92
18	Ph	Ph	30	90	35	90	70	88	70	85
19	Ph	NO_2-Ph	10[c]	15	10[c]	10	12[c]	10	12[c]	10

[a]Minutes.
[b]Isolated yield (%).
[c]In hours.

both solvent and solvent-free conditions. These results show that there was no steric effect from the substituents at anhydride moiety. Comparisons between the results of Tables 2 and 3 show that carboxylic acid anhydrides were found to be more reactive than carboxylic acid chlorides. Also, N-acylation of sulfonamides with electron-withdrawing groups containing carboxylic acid anhydrides needed a longer reaction time to form *N*-acylsulfonamides. For example, the reaction of benzenesulfonamide with 4-nitrobenzoic anhydride did not proceed well, and only 10–15% of product was obtained after 10–12 h (Table 2, entry 19). These results show that the acylinium ion was formed and then reacted with sulfonamide. This fact was further supported by N-acylation of benzenesulfonamide with benzoic-4-nitrobenzoic anhydride. After completion of the reaction, we observed that the only product is *N*-benzoyl benzenesulfonamide. In fact, sulfonamide reacted with a carbonyl group to form more stable acylinium ions (Scheme 2). On the other hand, comparison between the results obtained in solution and those under solvent-free conditions show that reaction proceeded faster in solvent-free conditions, which is in agreement with the goals of

Table 3. N-Acylation of sulfonamides with carboxylic acid chloride in solvent or solvent-free conditions



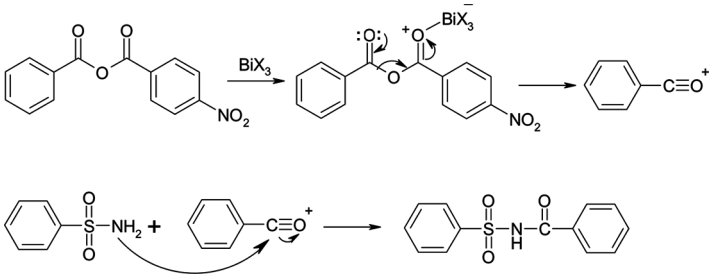
			Catalyst: $Bi(OTf)_3$ (5%)				Catalyst: $BiCl_3$ (10%)			
			Solvent-free		CH_2Cl_2		Solvent-free		$CHCl_3$	
Entry	R	R″	Time[a]	Yield[b]	Time[a]	Yield[b]	Time[a]	Yield[b]	Time[a]	Yield[b]
1	Ph	CH_3	3	92	5	91	16	88	17	87
2	Ph	C_2H_5	5	95	5	96	14	88	15	90
3	Ph	Ph	15	91	40	95	45	90	45	85
4	CH_3-Ph	CH_3	3	90	5	86	10	89	12	90
5	CH_3-Ph	C_2H_5	7	95	5	92	10	89	10	89
6	CH_3-Ph	Ph	20	90	45	85	50	80	55	83
7	CH_3	CH_3	1	94	5	95	10	90	12	88
8	CH_3	C_2H_5	1	95	1	94	10	92	10	90
9	CH_3	Ph	10	98	25	93	30	85	35	88

[a]Minutes.
[b]Isolated yield (%).

green chemistry. Furthermore, the experimental results show that $Bi(OTf)_3$ is more reactive and works better than $BiCl_3$ in terms of amount of catalyst, temperature, reaction times, and the yields of products (Tables 1–3).

Antimicrobial Activity

The test compounds were evaluated for their antibacterial activity against three Gram-positive cocci [*Staphylococcus aureus* ATCC 25922, clinical strains of *Staphylococcus aureus* VISA (vancomycin intermediate *Staphylococcus aureus*), and *Enterococcus faesium*), three Gram-negative bacilli (*Pseudomonas aeruginosa* ATCC 27853, clinical strains of *Klebsiella pneumonia*, and *Escherichia coli*), and the yeast (clinical strains of *Candida albicans*) using the microbroth-dilution



Scheme 2. N-Acylation of benzenesulfonamide with benzenoic-4-nitrobenzoic anhydride.

Table 4. MICs (in μg/mL) values of *N*-acylsulfonamides against bacteria and fungi

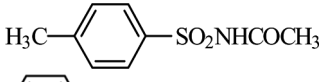
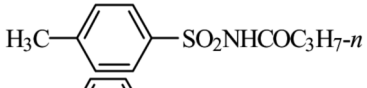
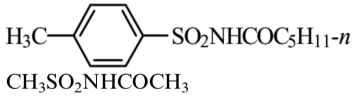
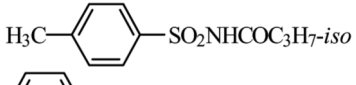
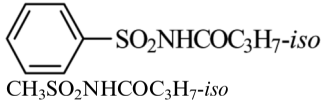
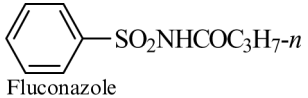
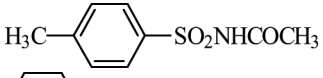
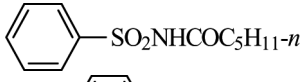
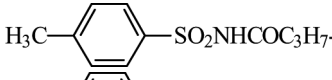
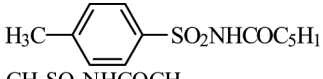
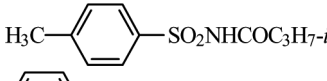
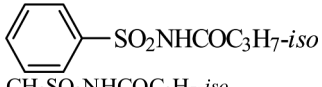
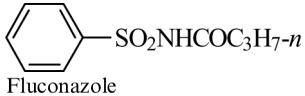
Compound	*E. coli* (clinically isolated)	*E. faecium* (clinically isolated)	*K. pneumoniae* (clinically isolated)	*S. aureus* VISA (clinically isolated)	*S. aureus* ATCC 25922	*P. aeruginosa* ATCC 27853	*Candida albicans* (clinically isolated)
	256	32	512	—	32	512	64
	512	32	512	—	32	256	128
	512	64	128	—	32	512	256
	512	32	—	—	32	512	512
$CH_3SO_2NHCOCH_3$	512	64	—	512	128	512	512
	128	512	512	512	256	256	512
	512	64	—	—	256	512	512
$CH_3SO_2NHCOC_3H_7$-*iso*	512	512	—	—	256	512	1024
	512	256	—	—	512	512	512
Fluconazole	—	—	—	—	—	—	4
Ciprofloxacin	4	4	8	2	4	4	—
Gentamicin	4	8	2	8	4	4	—
Sulfamethoxazole	2	4	8	4	2	8	—
Ceftriaxone	32	8	16	8	4	16	—

Table 5. Inhibition zone of *N*-acylsulfonamides against bacteria and fungi (in mm)

Compound	*E. coli* (clinically isolated)	*E. faecium* (clinically isolated)	*K. pneumoniae* (clinically isolated)	*S. aureus* VISA (clinically isolated)	*S. aureus* ATCC 25922	*P. aeruginosa* ATCC 27853	*Candida albicans* (clinically isolated)
	15	10	10	15	13	10	11
	18	15	12	10	25	14	13
	14	20	10	—	18	12	17
	15	14	9	—	30	—	15
$CH_3SO_2NHCOCH_3$	14	17	—	—	10	10	13
	—	15	—	14	30	—	14
	12	13	8	15	18	—	14
$CH_3SO_2NHCOC_3H_7$-*iso*	15	14	15	15	20	—	15
	10	13	12	—	29	12	10
Fluconazole	—	—	—	—	—	—	17
Gentamicin	20	20	20	20	25	18	—
Co-trimoxazole	21	—	—	20	18	22	—
Cefoxitin	20	18	18	14	16	15	—
Imipenem	30	25	25	23	30	25	—
Azithromycin	27	—	17	27	27	2	—
Tetracycline	—	—	15	25	30	20	—

method.[31] The obtained MIC (minimum inhibitory concentration) values were compared to gentamicin, ciprofloxacin, sulfamethoxazole, ceftriaxone, and fluconazole as the reference drugs and are presented in Table 4. Inhibition zones were determined by the disc diffusion method[32] and compared with fluconazole (25 μg), gentamicin (10 μg), co-trimoxazole (1.25:23.75 μg), cefoxitin (30 μg), imipenem (10 μg), tetracycline (30 μg), and azithromycin (15 μg) as the reference drugs (Table 5).

Microbiological results showed that the tested compounds possessed a broad spectrum of antibacterial activity against the screened microorganisms; however, they exhibited less antibacterial potency than the control drugs. The results reported in Table 4 indicate that the tested compounds are able to inhibit growth of the screened pathogens, showing MIC values between 32 and 1024 μg/mL. Among the synthesized compounds, *N*-ethanoyl methansulfonamide and *N*-isobutanoyl-4-methyl benzenesulfonamide were also potent against clinical VISA strains, showing an MIC value of 512 μg/mL. All the other compounds exhibited no antibacterial activity against the pathogens.

Moreover, the tested compounds also possessed antimycotic activity against the yeast *Candida albicans*, showing MIC values between 64 and 1024 μg/mL, whereas the antifungal potency of the compared control drug fluconazole was observed to be better than the corresponding compounds, showing an MIC value of 4 μg/mL. As seen in Table 5, *N*-butanoyl-4-methyl benzenesulfonamide shows the best antifungal activity against *C. albicans*, and its potency compares to that of the reference antibiotic (fluconazole).

CONCLUSION

In summary, we found that $Bi(OTf)_3$ and $BiCl_3$ are efficient catalysts for the N-acylation of different sulfonamides. This method offers several advantages, including mild reaction conditions, use of green catalysts, and no formation of bis-acylated by-products. Furthermore, this solvent-free protocol is a simple, inexpensive, safe, and ecofriendly alternative to the other methods for the N-acylation of sulfonamides. Also, antimicrobial activity of some of the synthesized sulfonamides demonstrated moderate to good inhibition against all the strains tested. Finally, these preliminary results are promising and are beneficial for further study in developing new compounds.

EXPERIMENTAL

General

All chemicals were purchased from Merck and Fluka chemical companies. The products were characterized by comparing the physical data with those of known samples or by their spectral data. Infrared (IR) spectra were recorded on Nicollet (impact 400D model) Fourier transform (FT)-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 300 Avance spectrophotometer in dimethylsulfoxide (DMSO-d_6) as the solvent and tetramethylsilane

(TMS) as internal standard. Column chromatography was performed using silica gel 60 (230–400 mesh). All yields refer to isolated yield.

General Procedure for N-Acylation of Sulfonamides Under Solvent-Free Conditions

Carboxylic acid chloride (2 mmol) or carboxylic acid anhydride (2 mmol) were added to a vigorously stirred mixture of sulfonamide (1 mmol) and $BiCl_3$ (0.1 mmol) or $Bi(OTf)_3$ (0.05 mmol) at room temperature. The progress of the reaction was monitored by thin-layer chromatography (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 and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (mixed EtOAc–petroleum ether as eluent) or recrystallized (toluene or ethyl acetate/*n*-hexane mixed solvent) to afforded the corresponding *N*-acyl sulfonamide in good to excellent yields.

General Procedure for N-Acylation of Sulfonamides in Solvent

A mixture of sulfonamide (1 mmol), carboxylic acid chloride (2 mmol), or carboxylic acid anhydride (2 mmol) was refluxed in $CHCl_3$ or CH_2Cl_2 (5 mL) in the presence of $BiCl_3$ (0.1 mmol) or $Bi(OTf)_3$ (0.05 mmol) for an appropriate time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, $CHCl_3$ or CH_2Cl_2 (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 as described for the solvent-free method.

Structural assignments of the products are based on their IR, ^{1}H NMR, ^{13}C NMR, and CHN analysis and also by comparison of their melting points with those of known compounds.

Spectral Data of Isolated *N*-Acylsulfonamides

***N*-Ethanoyl benzenesulfonamide (Table 2, entry 1).** Mp 120–122°C; IR υ (cm^{-1}): 3125, 2901, 1699, 1468, 1356, 1243, 1169, 867, 689; ^{1}H NMR (DMSO-d_6) δ (ppm) 1.92 (s, 3H), 7.59–7.73 (m, 3H), 7.91 (2H, dd, $J_1 = 7.2$ Hz, $J_2 = 1.5$ Hz) 12.10 (s, 1H);^{13}C NMR (DMSO-d_6) δ (ppm) 23.68, 127.90, 129.58, 134.08, 139.81, 169.23. (Found: C, 48.61; H, 4.77; N, 6.88. $C_8H_9NO_3S$ requires C, 48.23; H, 4.55; N, 7.03%.)

***N*-Propanoyl benzenesulfonamide (Table 2, entry 2).** Mp 75–76°C; IR ν (cm^{-1}): 3246, 2986, 1710, 1461, 1341, 1156, 845, 766, 595 cm^1; ^{1}H NMR (DMSO-d_6) δ (ppm) 0.88 (t, 3H, $J = 7.5$ Hz), 2.22 (q, 2H, $J = 7.5$ Hz), 7.59–7.70 (m, 3H), 7.91–7.94 (m, 2H), 12.06 (s, 1H);^{13}C NMR (DMSO-d_6) δ (ppm) 8.68, 29.15, 126.04, 127.87, 129.37, 129.56, 172.72. (Found: C, 50.88; H, 5.29; N, 6.68. $C_9H_{11}NO_3S$ requires C, 50.69; H, 5.20; N, 6.57%.)

***N*-Butanoyl benzenesulfonamide (Table 2, entry 3).** Mp 99–101°C; IR ν (cm^{-1}) 3216, 1687, 1608, 1330, 1171; ^1H NMR (DMSO-d_6) δ (ppm) 0.73 (t, 3H, $J = 7.3$ Hz), 1.41 (sext, 2H, $J = 7.3$ Hz), 2.16 (t, 2H, $J = 7.3$ Hz), 7.59–7.92 (m, 5H), 12.05 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 13.59, 17.94, 37.59, 127.86, 129.56, 134.05, 139.90, 171.96. (Found: C, 52.65; H, 5.59; N, 6.36. $C_{10}H_{13}NO_3S$ requires C, 52.85; H, 5.77; N, 6.16%.)

***N*-Pentanoyl benzenesulfonamide (Table 2, entry 4).** Mp 82–84°C; IR ν (cm^{-1}) 3101, 1688, 1608, 1350, 1164; ^1H NMR (DMSO-d_6) δ (ppm) 0.77 (t, 3H, $J = 7.2$ Hz), 1.13 (sext, 2H, $J = 7.4$ Hz), 1.37 (quin, 2H, $J = 7.4$ Hz), 2.19 (t, 2H, $J = 7.3$ Hz), 7.59–7.91 (m, 5H), 12.03 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 13.47, 21.31, 26.02, 34.97, 127.36, 129.04, 133.55, 139.38, 171.57. (Found: C, 54.92; H, 6.07; N, 5.68. $C_{11}H_{15}NO_3S$ requires C, 54.75; H, 6.27; N, 5.80%.)

***N*-Isobutanoyl benzenesulfonamide (Table 2, entry 5).** Mp 120–122°C; IR ν (cm^{-1}) 3257, 2979, 2880, 1719, 1434, 1335, 1176, 1090, 891, 758; ^1H NMR (DMSO-d_6) δ (ppm) 0.92 (d, 6H, $J = 6.8$ Hz), 2.45 (sept, 1H, $J = 6.8$ Hz), 7.59–7.91 (m, 5H), 12.07 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 18.83, 34.71, 127.81, 129.56, 134.04, 139.79, 175.75. (Found: C, 52.71; H, 5.89; N, 6.28. $C_{10}H_{13}NO_3S$ requires C, 52.85; H, 5.77; N, 6.16%.)

***N*-Benzoyl benzenesulfonamide (Table 2, entry 6).** Mp 137–139°C; IR ν (cm^{-1}): 3277, 3059, 1699, 1580, 1455, 1342, 1177, 1072, 900, 834, 575; ^1H NMR (DMSO-d_6) δ (ppm) 7.36–7.53 (m, 3H), 7.56–7.58 (m, 2H), 7.83–7.87 (m, 3H), 8.01–8.03 (m, 2H), 12.56 (s,1H);^{13}C NMR (DMSO-d_6) δ (ppm) 126.03, 128.12, 128.87, 129.07, 129.38, 129.60, 133.77, 134.12, 165.91. (Found: C, 59.95; H, 4.38; N, 5.21. $C_{13}H_{11}NO_3S$ requires C, 59.76; H, 4.24; N, 5.36%.)

***N*-Ethanoyl-4-methyl benzenesulfonamide (Table 2, entry 7).** Mp 136–138°C; IR ν (cm^{-1}) 3290, 1725, 1607, 1441, 1336, 1217, 1171, 867, 669 cm^1; ^1H NMR (DMSO-d_6) δ (ppm) 1.90 (s, 3H), 2.38 (s, 3H), 7.40 (d, 2H, $J = 8$ Hz), 7.79 (d, 2H, $J = 8.0$ Hz), 12.01 (s, 1H); ^1H NMR (DMSO-d_6) δ (ppm) 21.50, 23.64, 128.00, 129.96, 136.96, 144.62, 169.13. (Found: C, 51.01; H, 5.37; N, 6.57. $C_9H_{11}NO_3S$ requires C, 50.69; H, 5.20; N, 6.57%.)

***N*-Propanoyl-4-methyl benzenesulfonamide (Table 2, entry 8).** Mp 104–106°C; IR ν (cm^{-1}) 3143, 1715, 1596, 1344, 1191; ^1H NMR (DMSO-d_6) δ (ppm) 0.87 (t, 3H, $J = 7.5$ Hz), 2.20 (q, 2H, $J = 7.5$ Hz), 2.38 (s, 3H), 7.41 (d, 2H, $J = 8.1$ Hz), 7.79 (d, 2H, $J = 8.1$ Hz), 11.96 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 8.70, 21.50, 29.10, 127.97, 129.93, 137.09, 144.56, 172.61. (Found: C, 52.61; H, 5.87; N, 6.36. $C_{10}H_{13}NO_3S$ requires C, 52.85; H, 5.77; N, 6.16%.)

***N*-Butanoyl-4-methyl benzenesulfonamide (Table 2, entry 9).** Mp 79–81°C; IR ν (cm^{-1}) 3090, 1680, 1601, 1349, 1158; ^1H NMR (DMSO-d_6) δ (ppm) 0.74 (t, 3H, $J = 7.3$ Hz), 1.40 (sext, 2H, $J = 7.3$ Hz), 2.15 (t, 2H, $J = 7.3$ Hz), 2.38 (s, 3H), 7.4 (d, 2H, $J = 8.1$ Hz), 7.79 (d, 2H, $J = 8.1$ Hz), 11.97 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 13.60, 17.96, 21.49, 37.59, 127.95, 129.93, 137.08, 144.55, 171.85. (Found: C, 54.63; H, 6.21; N, 5.97. $C_{11}H_{15}NO_3S$ requires C, 54.75; H, 6.27; N, 5.80%.)

***N*-Pentanoyl-4-methyl benzenesulfonamide (Table 2, entry 10).** Mp 88–89°C; IR ν (cm^{-1}) 3271, 2960, 2868, 1719, 1593, 1428, 1342, 1151, 854; ^1H NMR (DMSO-d_6) δ (ppm) 0.76 (t, 3H, $J = 7.3$ Hz), 1.15 (sext, 2H, $J = 7.5$ Hz), 1.36 (quint, 2H, $J = 7.5$ Hz), 2.17 (t, 2H, $J = 7.3$ Hz), 2.37 (s, 3H), 7.4 (d, 2H, $J = 8$ Hz), 7.79 (d, 2H, $J = 8$ Hz), 11.96 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm); ^{13}C NMR (DMSO-d_6) δ (ppm) 13.94, 21.47, 21.83, 26.52, 35.46, 127.95, 129.90, 137.07, 144.51, 171.95. (Found: C, 56.78; H, 6.89; N, 5.33. $C_{12}H_{17}NO_3S$ requires C, 56.45; H, 6.71; N, 5.49%.)

***N*-Isobutanoyl-4-methyl benzenesulfonamide (Table 2, entry 11).** Mp 110–112°C; IR ν (cm^{-1}) 3259, 1731, 1329, 1171; ^1H NMR (DMSO-d_6) δ (ppm) 0.92 (d, 6H, $J = 6.8$ Hz), 2.38 (s, 3H), 2.41–2.46 (m, 1H,), 7.40 (d, 2H, $J = 7.8$ Hz), 7.78 (d, 2H, $J = 7.8$ Hz), 11.99 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 16.92, 19.57, 32.75, 125.97, 128.03, 135.03, 142.61, 173.72. (Found: C, 54.60; H, 6.41; N, 5.62. $C_{11}H_{15}NO_3S$ requires C, 54.75; H, 6.27; N, 5.80%.)

***N*-Benzoyl-4-methyl benzenesulfonamide (Table 2, entry 12).** Mp 145 – 147°C; IR ν (cm^{-1}) 3292, 3065, 1699, 1605, 1500, 1421, 1342, 1176, 897, 712, ^1H NMR (DMSO-d_6) δ (ppm) 2.38 (s, 3H), 7.42–7.63(m, 5H), 7.84–7.91 (m, 4H), 12.48 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 21.53, 128.22, 128.84, 129.06, 129.99, 131.94, 133.71, 137.02, 144.72, 165.83. (Found: C, 59.98; H, 4.61; N, 5.35. $C_{14}H_{13}NO_3S$ requires C, 61.07; H, 4.76; N, 5.09%.)

***N*-Ethanoyl methanesulfonamide (Table 2, entry 13).** Mp 97–98°C; IR ν (cm^{-1}) 3138, 2907, 1706, 1468, 1341, 1243, 1158, 874, 755, 590, 509; ^1H NMR (DMSO-d_6) δ (ppm) 1.99 (s, 3H), 3.21 (s, 3H), 11.67 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.70, 41.38, 170.25. (Found: C, 26.22; H, 5.21; N, 10.01. $C_3H_7NO_3S$ requires C, 26.27; H, 5.14; N, 10.21%.)

***N*-Propanoyl methanesulfonamide (Table 2, entry 14).** Mp 68–70°C; IR ν (cm^{-1}) 3143, 1687, 1343, 1158; ^1H NMR (DMSO-d_6) δ (ppm) 0.99 (t, 3H, $J = 7.5$ Hz), 2.27 (q, 2H, $J = 7.5$ Hz), 3.21 (s, 3H), 11.63 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 8.84, 29.16, 43.58, 173.72. (Found: C, 31.54; H, 6.21; N, 9.08. $C_4H_9NO_3S$ requires C, 31.78; H, 6.00; N, 9.26%.)

***N*-Butanoyl methanesulfonamide (Table 2, entry 15).** Mp 68–70°C; IR ν (cm^{-1}) 3203, 1700, 1330, 1151; ^1H NMR (DMSO-d_6) δ (ppm) 0.86 (t, 3H, $J = 7.3$ Hz), 1.53 (sext, 2H, $J = 7.3$ Hz), 2.23 (t, 2H, $J = 7.3$ Hz), 3.22 (s, 3H), 11.64 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 13.22, 17.50, 37.14, 40.88, 172.46. (Found: C, 36.61; H, 6.51; N, 8.78. $C_5H_{11}NO_3S$ requires C, 36.35; H, 6.71; N, 8.84%.)

***N*-Pentanoyl methanesulfonamide (Table 2, entry 16).** Mp 69–71°C; IR ν (cm^{-1}) 3269, 1720, 1330, 1158; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm) 0.86 (t, 3H, $J = 7.3$ Hz), 1.26 (sext, 2H, $J = 7.4$ Hz), 1.48 (quin, 2H, $J = 7.4$ Hz), 2.25 (t, 2H, $J = 7.3$ Hz), 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. (Found: C, 39.98; H, 7.22; N, 7.97. $C_6H_{13}NO_3S$ requires C, 40.21; H, 7.31; N, 7.81%.)

***N*-Isobutanoyl methanesulfonamide (Table 2, entry 17).** Mp 97–99°C; IR ν (cm^{-1}) 3213, 1717, 1329, 1158; ^1H NMR (DMSO-d_6) δ (ppm) 1.03 (d, 6H,

$J = 6.8$ Hz), 2.49 (sept, 1H, $J = 6.9$ Hz), 3.22 (s, 3H), 11.64 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 19.05, 34.73, 41.32, 176.85. (Found: C, 36.32; H, 6.83; N, 8.67. $C_5H_{11}NO_3S$ requires C, 36.35; H, 6.71; N, 8.84%.)

***N*-Benzoyl methanesulfonamide (Table 2, entry 18).** Mp 153–155°C; IR ν (cm^{-1}) 3244, 1692, 1335, 1177; ^{1}H NMR (DMSO-d_6) δ (ppm) 3.38 (s, 3H), 7.49–7.95 (m, 5H), 12.14 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 41.78, 128.90, 129.00, 132.11, 133.70, 166.92. (Found: C, 48.58; H, 4.67; N, 6.86. $C_8H_9NO_3S$ requires C, 48.23; H, 4.55; N, 7.03%.)

Biological Assays

Turbidity of all the bacterial cultures was adjusted to 0.5 McFarland standard by preparing a bacterial suspension of three to five 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 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 distilled water (4.5 mL) to get a stock solution of 10000 mg/mL of each compound. Further progressive double dilution with Muller–Hinton broth was performed to obtain the required concentrations of 1024, 512, 256, 128, 64, 32, 16, 8, 4, and 2 μg/mL.[31] To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilutions as used in the experiment. Our results indicated that all the compounds tested in this study demonstrated less activity against both Gram-positive and Gram-negative microorganisms than the reference drug.

Standard antibiotics were 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 suspention was added. After overnight incubation in 37°C, growth was surveyed. Data of MICs of the test compounds and control drugs are shown in Table 4.

Inhibition zones of compounds were determined by the disc diffusion method.[32] The antimicrobial screening was surveyed using the sterilized (autoclaved at 120°C for 30 min) Mueller–Hinton Agar and YEPD agar for the yeast. The culture suspensions were prepared and adjusted by comparing against 0.5 McFarland turbidity tubes. Mueller–Hinton and YEPD agar were poured into each sterile Petri dish. After the media were solidified, the bacteria were cultured using sterile swabs. All of the compounds were dissolved in DMSO of 10 mg/mL. Empty sterilized discs of 6.4 mm (Padtan Teb, Iran) were impregnated with 100 μL of compounds. Discs were placed on agar plates, and the cultures were incubated at 37°C for 24 h for bacteria and 48 h for *C. albicans*. Inhibition zones formed on the medium were evaluated in millimeters. The solvent control (DMSO) did not show any antimicrobial activity. Inhibition zones were compared with those of reference discs. Reference discs used for control are as follows: fluconazole (25 μg), gentamicin (10 μg), co-trimoxazole (1.25:23.75 μg), cefoxitin (30 μg), imipenem (10 μg), tetracycline (30 μg), and azithromycin (15 μg).

ACKNOWLEDGMENTS

We thank Dr. Taki for his kind help and the Islamic Azad University of Shahreza Research Council for their partial support. We gratefully acknowledge the Kermanshah University of Medical Sciences Research Council for financial support.

REFERENCES

1. Padmavathi, V.; Thriveni, P.; Sudhakar Reddy, G.; Deepti, D. Synthesis and antimicrobial activity of novel sulfone-linked bis-heterocycles. *Eur. J. Med. Chem.* **2008**, *43*, 917.
2. Kim, S. J.; Park, H. B.; Lee, J. S.; Jo, N. H.; Yoo, K. H.; Baek, D.; Kang, B.; Cho, J. H.; Oh, C. H. Novel lβ-methylcarbapenems having cyclic sulfonamide moieties: Synthesis and evaluation of in vitro antibacterial activity. *Eur. J. Med. Chem.* **2007**, *42*, 1176.
3. Hasegawa, T.; Yamamoto, H. A practical synthesis of optically active (*R*)-2-propyloctanoic acid: Therapeutic agent for Alzheimer's disease. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 423.
4. Banwell, M. G.; Crasto, C. F.; Easton, C. J.; Forrest, A. K.; Karoli, T.; March, D. R.; Mensah, L.; Nairn, M. R.; O'Hanlon, P. J.; Oldham, M. D.; Yue, W. Analogues of SB-203207 as inhibitors of tRNA synthetases. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2263.
5. Wang, Y.; Soper, D.; Dirr, M. J.; deLong, M. A.; De, B.; Wos, J. A. The synthesis and human FP receptor binding affinity of 13,14-dihydro prostaglandin $F_{1\alpha}$ sulfonamides: Potential treatments for osteoporosis. *Chem. Pharm. Bull.* **2000**, *48*, 1332.
6. Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Chen, T. B.; O'Malley, S. S.; Zingaro, G. J.; Siegl, P. K. S.; Kivlighn, S. D.; Lotti, V. J.; Chang, R. S. L.; Greenless, W. J. Triazolinone biphenylsulfonamides as angiotensin I1 receptor antagonists with high affinity for both the AT1 and AT2 subtypes. *J. Med. Chem.* **1994**, *37*, 4464.
7. Musser, J. H.; Kreft, A. F.; Bender, R. H. W.; Kubrak, D. M.; Grimes, D.; Carlson, R. P.; Hand, J. M.; Chang, J. *N*-[(Arylmethoxy)phenyl] carboxylic acids, hydroxamic acids, tetrazoles, and sulfonyl carboxamides: Potent orally active leukotriene D4 antagonists of novel structure. *J. Med. Chem.* **1990**, *33*, 240.
8. Kondo, K.; Sekimoto, E.; Nakao, J.; Murakami, Y. Studies on development of sufficiently chemoselective N-acylation reagents: *N*-Acyl-*N*-(2,3,4,5,6-pentafluorophenyl)methanesulfonamides. *Tetrahedron* **2000**, *56*, 5843.
9. Kondo, K.; Sekimoto, E.; Miki, K.; Murakami, Y. A versatile synthon for chemoselective N-acylation reagents, 2-fluoro-*N*-mesylaniline. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 2973.
10. Ellis, D. Racemisation-free synthesis of chiral acylsulfonamides. *Tetrahedron: Asymmetry* **2001**, *12*, 1589.
11. Juteau, H.; Gareau, Y.; Labelle, M.; Sturino, C. F.; Sawyer, N.; Tremblay, N.; Lamontagne, S.; Carriere, M. C.; Denis, D.; Metters, K. M. Structure–activity relationship of cinnamic acylsulfonamide analogues on the human EP_3 prostanoid receptor. *Bioorg. Med. Chem.* **2001**, *9*, 1977.
12. Ishizuka, N.; Matsumura, K. I.; Hayashi, K.; Sakai, K.; Yamamori, T. An efficient method for the preparation of enantiomerically pure *N*-acylarylsulfonamides having an asymmetric center at the α-position: Condensation of acid chlorides and arylsulfonamides under solid–liquid two-phase conditions. *Synthesis* **2000**, 784.
13. Ishizuka, N.; Matsumura, K. I. Process for preparation of optically active acyl sulfone amides. Japanese Patent JP-10045705, 1998.
14. Inoe, T.; Myahara, O.; Takahashi, A.; Nakamura, Y. Preparation of N-substituted-N-sulfonylamides from sulforylamides and acyl compounds. Japanese Patent JP-08198840, 1996.

15. Massah, A. R.; Azadi, D.; Aliyan, H.; Momeni, A. R.; Javaherian Naghash, H.; Kazemi, F. An efficient method for the synthesis of *N*-acylsulfonamides: One-pot sulfonylation and acylation of primary arylamines under solvent-free conditions. *Monatsh. Chem.* **2008**, *139*, 233.
16. Morisawa, Y.; Kataoka, M.; Negahori, H.; Sakamoto, T.; Kianto, N.; Kusano, K. Studies on anticoccidial agents: Synthesis and anticoccidial activity of nitropyridine-2- and -3-sulfonamides and derivatives. *J. Med. Chem.* **1980**, *23*, 1376.
17. Martin, M. T.; Roschangar, F.; Eaddy, J. F. Practical acid-catalyzed acylation of sulfonamides with carboxylic acid anhydrides. *Tetrahedron Lett.* **2003**, *44*, 5461.
18. Singh, D. U.; Singh, P. R.; Samant, S. D. Fe-exchanged montmorillonite K10—The first heterogeneous catalyst for acylation of sulfonamides with carboxylic acid anhydrides. *Tetrahedron Lett.* **2004**, *45*, 4805.
19. Massah, A. R.; Momeni, A. R.; Dabagh, M.; Aliyan, H.; Javaherian Naghash, H. Facile synthesis of *N*-acylsulfonamide in the presence of silica chloride (SiO_2-Cl) both under heterogeneous and solvent-free conditions. *Synth. Commun.* **2008**, *38*, 265.
20. Massah, A. R.; Dabagh, M.; Afshar, M.; Momeni, A. R.; Aliyan, H.; Javaherian Naghash, H. A convenient and efficient synthesis of *N*-acylsulfonamides in the presence of silica phosphoric acid under heterogeneous and solvent-free conditions. *Turk. J. Chem.* **2007**, *31*, 611.
21. Suzuki, H.; Matano, Y. *Organobismuth Chemistry*; Elsevier: Amsterdam, 2001.
22. Gaspard-Iloughmane, H.; Le Roux, C. Bismuth(III) triflate in organic synthesis. *Eur. J. Org. Chem.* **2004**, *69*, 2517.
23. Leonard, N. M.; Wieland, L. C.; Mohan, R. S. Applications of bismuth(III) compounds in organic synthesis. *Tetrahedron* **2002**, *58*, 8373.
24. Ollevier, T.; Lavie-Compin, G. Bismuth triflate–catalyzed mild and efficient epoxide opening by aromatic amines under aqueous conditions. *Tetrahedron Lett.* **2004**, *45*, 49.
25. Ollevier, T.; Nadeau, E. Bismuth triflate–catalyzed three-component Mannich-type reaction. *J. Org. Chem.* **2004**, *69*, 9292.
26. Le Roux, C.; Ciliberti, L.; Laurent-Robert, H.; Laporterie, A.; Dubac, J. Bismuth(III) triflate: A water-stable equivalent of trimethylsilyl triflate for the catalysis of Mukaiyama aldol reactions. *Synlett* **1998**, 1249.
27. Ollevier, T.; Mwene-Mbeja, T. M. Bismuth triflate–catalyzed Claisen rearrangement of allyl naphthyl ethers. *Tetrahedron Lett.* **2006**, *47*, 4051.
28. Mohammadpoor-Baltork, I.; Aliyan, H. Bismuth(III) chloride, a mild and efficient catalyst for synthesis of thiiranes from oxiranes. *Synth. Commun.* **1999**, *29*, 2741.
29. Mohammadpoor-Baltork, I.; Aliyan, H.; Khosropour, A. R. Bismuth(III) salts as convenient and efficient catalysts for the selective acetylation and benzoylation of alcohols and phenols. *Tetrahedron* **2001**, *57*, 5851.
30. Massah, A. R.; Kazemi, F.; Azadi, D.; Farzaneh, S.; Aliyan, H.; Javaherian Nagash, H.; Momeni, A. R. A mild and chemoselective solvent-free method for the synthesis of *N*-aryl and *N*-alkylsulfonamides. *Lett. Org. Chem.* **2006**, *3*, 235.
31. Baron, E. J.; Finegold, S. M. In *Bailey and Scott's Diagnostic Microbiology*; C. V. Mosby (Ed.), 8th ed.; St. Louis, 1990; pp. 184–188.
32. National Committee for Clinical Laboratory Standards (NCCLS). *Approved Standard Document M-7A*; NCCLS: Villanova, PA, 1985.