Effect of Microwave-Assisted on the *N*-Alkylation and *N*-Acylation of Cyclic Sulfamides.

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RESUMÉ : Les sulfamides cycliques sont *N*-acylés et *N*-alkylés de manière efficace avec différents groupes alkyle, benzyle et halogénures d'acyles. Les réactions ont été réalisées dans des conditions d'irradiation par micro-ondes avec ou sans solvant. Une comparaison avec les méthodes classiques démontre les avantages de l'application des micro-ondes comme une méthode non-classique d'activation en synthèse organique et les transformations chimiques. Les structures des composés synthétisés ont été identifiées grâce à leurs données analytiques et spectrales.

MOTS-CLÉS : Micro-ondes ; Sulfamides cycliquies ; halogénure d'alkyle ; halogénures d'acyles ; *N*-alkylation ; *N*-acylation.

ABSTRACT: Cyclic sulfamides were efficiently *N*-acylated and *N*-alkylated with different alkyl, benzyl and acylhalides. The reactions were carried out under microwave irradiation conditions with and without solvent. A comparison with conventional methods demonstrates the advantages of applying microwave irradiation as a non-conventional method for activation in organic syntheses and chemical transformations. The structures of the synthesized compounds were inferred from their analytical and spectral data.

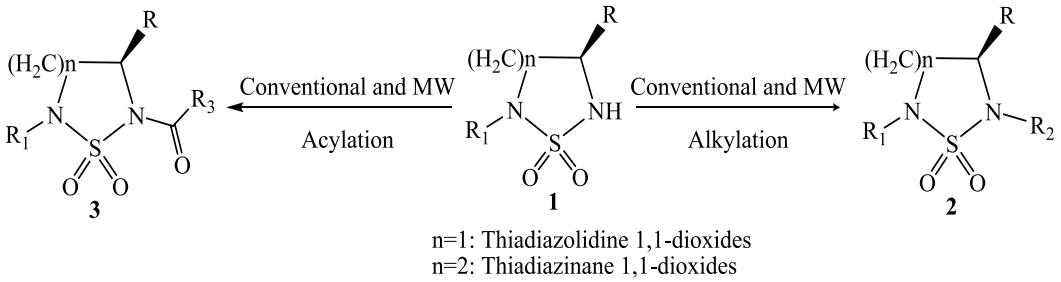
KEYWORD: Microwave; Cyclic sulfamides; alkyl halide; acyl halide; *N*-alkylation; *N*-acylation.

1. Introduction

Sulfamide-containing-heterocycles (cyclic sulfamides) are of great interest because of their manifold applications as intermediates for biologically active molecules. Many products that contain a sulfamide moiety exhibit biological activity such as anti-HIV protease [1] and some serving as metalloprotease inhibitors [2] and nonhydrolyzable peptidomimetics [3].

In recent years, 1,2,5-thiadiazolidine 1,1-dioxide compounds **1**, **2** and **3** have been among the most extensively investigated classes of organic compounds, with a wide spectrum of biological activity [4-6]. These compounds are known to inhibit several families of enzymes, including serine proteases [7-8], γ-secretases [9] and constrained peptides [10-11]. Additionally, fused heterocyclic derivatives with the thiadiazolidine moiety are also used as drug and pesticide intermediates.

Considering the biological importance of *N*-substituted cyclic sulfamides and our interest in environmentally chemical transformations [12], we report in this paper the results of our studies on *N*-acylation and *N*-alkylation of non-*N*-substituted cyclic sulfamides using microwave irradiation with and without solvent. The application of this methodology has become sustainable and powerful tool in chemical synthesis, since by using this technique of activation it is possible to synthesize organic compounds with high purity and in better yields, compared with other conventional methods [13-16]. The synthetic pathways are depicted in Scheme 1. Starting materials ***1a -1q*** were prepared according to published procedures [17-20].

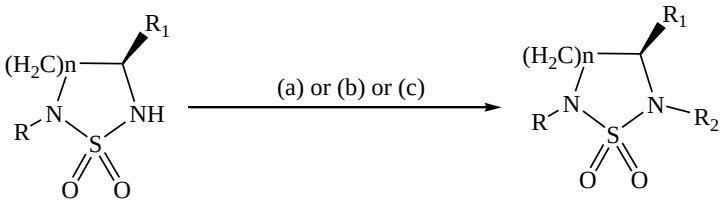


Scheme 1: Synthetic route for *N*-alkylation and *N*-acylation of cyclic sulfamide derivatives.

2. Results and Discussion

2.1. *N*-Alkylation

The series of alkylated cyclic sulfamides (N^5-alkyl-1,2,5-thiadiazolidine and N^6-alkyl-1,2,6-thiadiazinane) ***2a -2q*** was conventionally prepared similar to previous descriptions [21-22]. This was done by refluxing solutions of different cyclic sulfamides ***1a -1p*** and various alkylating agents for 4 to 5 hours, in the presence of a base catalyst in a suitable organic solvent. The results are summarized in Table 1.

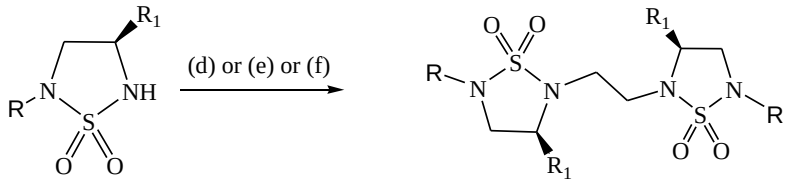


1a: n=1, R= Boc, R_1= H; **1b**: n=1, R= Boc, R_1= iPr
1c: n=1, R= Boc, R_1= Me;**1d**: n=1, R= Boc, R_1=iBu
1e: n=1, R= COOMe, R_1=H;**1f**: n=1, R= COOMe, R_1= Bn
1g: n=1, R= Me, R_1= H; **1h**: n=1, R= $CH_3CHCOOMe$, R_1= H
1i: n=1, R= Et(CH)COOMe, R_1= H; **1j**: n=1, R= Pr(CH)COOMe, R_1= H
1k: n=1, R= 3-nitrophenyl, R_1= H; **1l**: n=1, R= iBu(CH)COOMe, R_1= H
1m: n=1, R= iPr(CH)COOMe, R_1= H; **1n**: n=2, R= Boc, R_1= H
1o: n=2, R= COOMe, R_1= H

(a) Conventionnal: solvent, base, alkylating agent (R-X: X= Cl, Br); (b) µW: H_2O, base, alkylating agent (R-X: X= Cl, Br);(c) µW-solvent-free: base, alkylating agent (R-X: X= Cl, Br).

Scheme 2: Reaction scheme for *N*-alkylation of cyclic sulfamides.

From the results shown in Table 1 it can be seen that the similar reaction of non-*N*-substituted cyclic sulfamides with alkyl *di*-halide (1,2-dibromoethane) gave N^5,$N^{5'}$-(éthane-1,2-diyl)bis(1,2,5-thiadiazolidine-2-carboxylate) ***2j*** and ***2k*** in 88% and 86% yields, respectively.



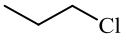
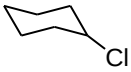
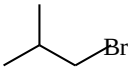
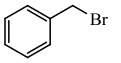
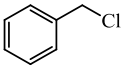
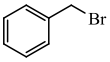
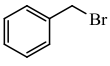
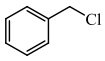
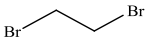
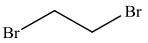
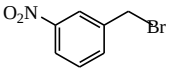
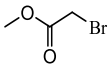
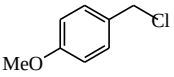
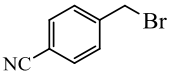
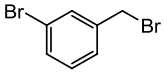
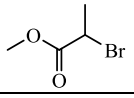
1a: R= Boc, R_1= H
1e: R= COOMe, R_1=H

2j: R= Boc, R_1= H
2k: R= COOMe; R_1= H

(d) Conventionnel: K_2CO_3, 1,2-dibromoethane, acetone, reflux, 4-5h; (e) µW: Acetone (2 mL) , K_2CO_3, 1,2-dibromoethane; (f) µW-solvent-free: K_2CO_3, 1,2-dibromethane.

Scheme 3: *N*-Alkylation of N^5H-1,2,5-thiadiazolidine 1,1-dioxides with alkyl di-halides.

Table 1: Reaction times and yields for *N*-alkylation of cyclic sulfamides under microwave irradiation and conventional heating.

Comp/Ref	*Entry/Ref*	*Alkylating agent*	*Conventional*			*µWI in* solvent *300W,100°C*		*µWI - Solvent-free 300W,110°C*	
			Solvent Base	*Time/T (h/°C)*	*Yield %*	*Time min*	*Yield %*	*Time (min)*	*Yield %*
2a[18]	***1a***[18]		CH_3CN K_2CO_3	4/90	77	05	90	04	94
2b[18]	***1n***[18]		DMF K_2CO_3	4/130	80	05	88	04	90
2c[18]	***1a***		H_2O K_2CO_3	4/110	66	05	90	04	87
2d[18]	***1a***		Dioxane K_2CO_3/NaOH	5/100	79	04	81	04	88
2e[18]	***1n***		CH_3CN Cs_2CO_3	3/90	81	04	96	03	90
2f[18]	***1a***		DMSO K_2CO_3	3/120	80	04	94	03	92
2g[18]	***1d***[8]		DMF K_2CO_3	3/130	82	04	98	03	91
2h[17]	***1e***[20]		DMF Cs_2CO_3	3/130	84	04	95	03	88
2i[18]	***1c***[18]		DMF K_2CO_3	3/130	81	05	93	03	88
2j[17]	***1a***		Acetone K_2CO_3	5/60	88	06	91	08	90
2k[17]	***1e***		CH_3CN Cs_2CO_3	5/90	86	05	94	06	91
2l[17]	***1e***		DMF K_2CO_3	4/130	87	05	93	04	90
2m[29]	***1a***		H_2O Cs_2CO_3	4/100	80	05	91	04	90
2n[17]	***1o***[20]		DMF K_2CO_3/KOH	3/130	84	04	91	04	94
2o[17]	***1o***		Acetone K_2CO_3	5/70	80	04	97	04	94
2p[17]	***1o***		DMSO Cs_2CO_3	5/100	89	04	91	04	93
2q[29]	***1a***		Acetone K_2CO_3	5/70	81	05	92	03	90

In continuation of our research on the development of simple methods for the synthesis of useful compounds, we report a novel method for the *N*-alkylation of cyclic sulfamides with alkyl halides with a route using microwave irradiation [23]. The results in Table 1 indicate the isolation of products ***2a-2q*** using three methods, however in different yields.

Using a microwave oven as the energy source, we optimized the reaction conditions of alkylation by testing different parameters such as different bases and solvents. The best results were obtained employing K_2CO_3 or Cs_2CO_3 in N, N-dimethylformamide (DMF) or acetonitrile (CH_3CN) [23]. As an example, with K_2CO_3/DMF, the alkylated product ***2g*** was obtained in good yield (98 %) in four minutes, whereas conventional process requires three hours. Moreover, the effects of solvents such as CH_3CN, DMF and basic aqueous medium (H_2O/base) were also studied (compounds ***2a***, ***2b*** and

2c). The yields of ***2a***, ***2b*** and ***2c*** were 90%, 88% and 90%, respectively. The results revealed that the solvents do not show any influence on the alkylation yield.

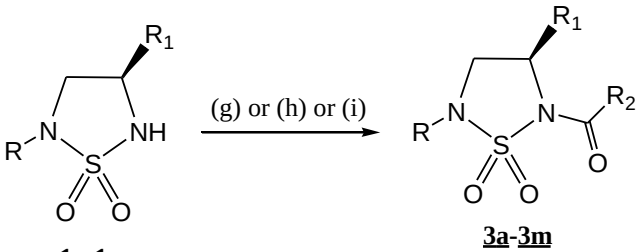
As is evident from Table 1, under MW conditions the reaction times decrease from several hours to five minutes, and the amount of solvent was reduced using microwave irradiation.

The nucleophilic substitution at the nitrogen atom of 1,2,5-thiadiazolidine 1,1-dioxides has also been achieved using microwave irradiation under solvent-free conditions [24]. The reactions were carried out by thoroughly mixing cyclic sulfamide with 2 equiv of an alkyl halide, catalytic amount (0.01 equiv) of tetra-butylammonium bromide and anhydrous potassium carbonate followed by irradiation in a microwave at 300 W for the given time (see Table 1) [25]. Extraction three times with methylene chloride and chromatographic purification on a silica gel column gave the *N*-alkylthiadiazolidine 1,1-dioxides dérivatives ***2a -2o*** in yields generally greater than 85% (Table 1). The Solvent-Free MWI protocols provides an opportunity to work with open vessels, thus avoiding the various risks and problems associated with the use of organic solvents [24].

2.2. *N*-Acylation of cyclic sulfamides

Conventional *N*-acylation reaction was carried out by treatment of non-*N*-substituted cyclic sulfamides (*N*^{5}*H*-1,2,5-thiadiazolidine and *N*^{6}*H*-1,2,6-thiadiazinane) with a series of acylating agents (acylchlorides, anhydrides or carboxylic acids) under basic conditions (Triethylamine, pyridine, dimethylaminopyridyne or NaH) (see Table 2). Another approach to the *N*-acylation of cyclic sulfamides utilizes concentrated H_2SO_4 in carboxylic acid anhydride as solvent (**3c**) or dry organic solvent such as CH_3CN or DMF (compounds ***3f*** and ***3k***) [8], [26-29].

To choose the suitable solvent for the acylation, the model reaction was tested in different solvents under thermal conditions. The results are shown in Table 2.

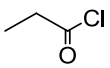
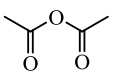
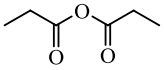


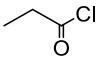
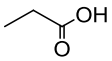
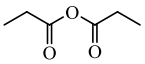
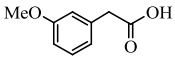
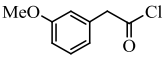
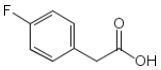
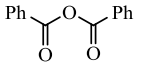
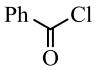
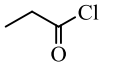
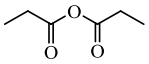
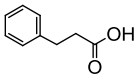
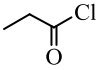
1g-**1p** **3a**-**3m**

(g) Conventionnel: solvent, base, acylating agent; (h) µW: solvent (2 mL), base, acylating agent; (i) µW-solvent-free: acylating agent, base.

Scheme 4: Reaction scheme for *N*-acylation of non-*N*^{5}-substituted cyclic sulfamides.

Table 2: Reaction times and yields for *N*-acylation of cyclic sulfamides under microwave irradiation with and without solvent and for conventional heating.

Comp	*Entry*	*Acylating Agent*	*Conventional*			*µWI in Solvent 300W, various T°C*		*µWI - Solvent-free 300W,110°C*	
			Solvent. Base	*Time/T (h/°C)*	*Yield %*	*Time (min/T)*	*Yield %*	*Time (min)*	*Yield %*
3a[26]	***1d***[26]		CH_2Cl_2 TEA	5/40	73	05	90	08	88
3b[26]	***1b***[26]		C_6H_6 TEA	3/80	80	03	94	05	92
3c[26]	***1b***		Acetic Anhydride conc H_2SO_4	4/80	85	3	96	3	93
3d[26]	***1d***[26]		PhMe C_5H_5N	4/100	70	05	89	10	90

3e[26]	***1a***		CH_2Cl_2 TEA	5/60	70	05	92	04	91
			CH_2Cl_2 TEA	5/70	35	04	85	05	71
3f	***1h***[29]		CH_3CN H_2SO_4	5/90	74	05	93	06	90
3g[8]	***1d***		PhMe not	10/100	31	03	80	10	72
			C_6H_6 TEA	3/80	71	03	96	05	91
3h[8]	***1d***		CH_2Cl_2 TEA	3/60	28	04	70	04	67
3i[8]	***1d***		THF K_2CO_3	3/70	78	02	96	05	84
			CH_2Cl_2 TEA	4/40	69	03	85	04	76
3j[29]	***1l***[29]		THF TEA/DMAP	4/70	82	05	94	05	90
3k[29]	***1m***[29]		DMF H_2SO_4	3.5/110	77	03	92	05	96
3l[8]	***1d***		PhMe TEA	4/90	36	05	70	05	59
3m[29]	***1j***[29]		THF NaH	4/70	81	04	93	05	91

However, most of the published protocols suffer from more disadvantages such as long reaction time, low yield of product and use of dangerous reagents and solvent.

Since the aim of our current research is concerned with achieving reasonable yields in the synthesis of substituted heterocyclic compounds which might have potential biological activities, compounds ***3a-3m*** (Table 2) were also obtained under microwave conditions following two methodologies [30]. First, we examined the *N*-acylation of non-*N*-substituted cyclic sulfamides with acylating agent using K_2CO_3 or H_2SO_4 in dry organic solvent under microwave irradiation (Table 2). The use of microwave irradiation was effective in that the reaction was completed within 2-10 minutes. In contrast, the reaction was completed (as monitored by thin-layer chromatography) in 4-5 hours in the case of classical heating (Table 2).

In order to find the best conditions for the formation of *N*-acylated cyclic sulfamides ***3a-3m***, the reactions were performed with microwave under solvent-free conditions. As indicated in Table 2, compounds ***3a-3m*** were obtained in high yields within short reaction times. The *N*-acylated products were obtained by simple cold aqueous work-up followed by extraction with methylene chloride and were finally chromatographed on silica gel column to afford pure *N*-acylated-cyclic sulfamides.

The enhanced reactivity under microwave irradiation was evident by comparison with the reactions under classical conditions (Table 2). *N*-Acylation under conventional heating conditions required longer reaction times and *N*-acylated cyclic sulfamides were obtained in lower yields, while the acylation under microwave irradiation gave higher purity and yields of the desired products in 3 to 10 minutes. This technique using microwave irradiation can be said to be a simple, improved and eco-friendly procedure to obtain *N*-acylated and *N*-alkylated cyclic sulfamide derivatives. The formation of products ***2a-2q*** and ***3a-3m*** was confirmed by interpretation of their FT-IR, ^{1}H-NMR and mass spectra.

3. Conclusion

We have presented a novel, highly rapid, efficient and solvent-free protocol for the *N*-acylation and *N*-alkylation of non-*N*-substituted cyclic sulfamide derivatives using a microwave oven as the irradiation source in organic solvent and aqueous medium and under solvent-free conditions. This study leads to a better understanding of *N*-alkylation and *N*-acylation of cyclic sulfamide derivatives. Further developments of this work and the evaluation of product biological activities are currently in progress.

4. Experimental

4.1. General

All commercial chemicals and solvents used were analytical grade and were used as received. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance spectrometer. Chemical shifts were reported in ppm with respect to internal TMS. Coupling constants (J) are quoted in Hz. Infrared spectra were recorded on a Shimadzu FT-IR 8400S spectrophotometer. The mass spectrometry data were obtained using a Hewlett Packard 5989 A instrument at 70 eV for the EI spectra and using methane as the reagent gas for CI spectra. Microwave irradiation was performed in a modified domestic microwave oven (Galanz WP-750B).

4.2. Conventional Heating Procedure for *N*-Alkylation of Cyclic Sulfamides.

To a stirring solution of non-N^5-substituted 1,2,5-thiadiazolidine 1,1-dioxides (cyclic sulfamides) ***1a-1m*** (1 equiv, 1 mmol) in dry organic solvent (CH_3CN, DMF,…) or H_2O (20 mL) in a 100mL round bottom flask was added K_2CO_3 (2.5 equiv, 2.5 mmol) or Cs_2CO_3 (2.5 equiv, 2.5 mmol). Alkylating agent, alkyl halide (1 equiv, 1 mmol) was added slowly and the resulting mixture was stirred at reflux for the appropriate time then cooled to room temperature. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with 2 portions of HCl 1M (2x10 mL), water (2x10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the crude oil. Flash chromatography on silica gel CH_2Cl_2 to furnish the pure *N*-alkyl-cyclic sulfamide in 65–85% yields the following.

4.3. Microwave-Assisted Procedure for *N*-Alkylation of Cyclic Sulfamides.

Compounds ***2a-2o*** were prepared according to previously published protocols [27]. To a stirred solution of non-*N5*-substituted-1,2,5-thiadiazolidine 1,1-dioxides (cyclic sulfamide) (1 eq, 1 mmol) and an appropriate alkyl halide (1.5 eq, 1.5 mmol) in appropriate solvent (2 ml), K_2CO_3 (2 mmol, 0.28 g) was added and the mixture was stirred at room temperature for 5 min. Then, the resulting mixture was placed in the microwave and irradiated at 300 W at 100 °C for an appropriate time (as reported in Table II (2 to 10 min). After completion (monitored by TLC), the reaction mixture was cooled, diluted with water (100 mL), neutralised with $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 mL); the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography using CH_2Cl_2 give the N^5-alkylated product.

4.4. Microwave-Assisted Solvent-Free Procedure for *N*-Alkylation of Cyclic Sulfamides.

Compounds **2a-2o** were prepared according to previously published protocol [25]. A mixture of non-N^5-substituted-1,2,5-thiadiazolidine 1,1-dioxides (1 equiv, 1 mmol), the appropriate alkyl halide (2 equiv, 2 mmol), base (4 equiv, 4 mmol) and catalytic amount of *tetra*-butylammonium bromide (TBAB) (0.01 equiv, 0.01 mmol) were mixed in an open conical flask and stirred for a few seconds. The mixture was placed inside the microwave oven, and irradiated at 300 W for the given time (Table 1). After completion of the reaction (monitored by TLC), the product is extracted with methylene chloride. The solvent was removed under reduced pressure and the residue was purified by column chromatography using CH_2Cl_2 to afford the corresponding N^5-alkylated-1,2,5-thiadiazolidine 1,1-dioxides product in yields typically greater than 80%.

4.5. Conventional Procedure for *N*-Acylation of Cyclic Sulfamides with Acyl Chlorides (for products *3a, 3b, 3e, 3g, 3i, 3j, 3l, 3l, 3m*). [12][26]

A solution of acyl chloride (1 equiv, 1 mmol) in dry organic solvent (10 mL) was added dropwise to a mixture of non-N^5-substituted-1,2,5-thiadiazolidine 1,1-dioxides ***1a-1h*** (1 equiv, 1 mmol) and triethylamine (1.2 equiv) in the same solvent 20 mL in round bottomed flasek and the reaction mixture was left to stir under reflux for 2 to 5 h (monitored by TLC). Upon completion of the reaction, the reaction mixture was cooled to room temperature and followed by solvent removal under reduced pressure. The residue was taken up in CH_2Cl_2, washed with $NaHCO_3$ (5%, 2x10 mL), brine (2x10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product. Flash chromatography on silica gel using ethyl acetate n-hexane (1:3) as the eluent afforded the corresponding pure *N5*-acyl-1,2,5-thiadiazolidine 1,1-dioxides.

4.6. Conventional Procedure for *N*-Acylation of Cyclic Sulfamides with Anhydrides (for products *3c, 3d, 3f, 3i, 3k*).

A mixture of non-N^5-substituted-1,2,5-thiadiazolidine 1,1-dioxides ***1a-1p*** (1 equiv, 1.0 mmol), carboxylic acid anhydride (1.5 mmol) and 2 drops of conc H_2SO_4 or three equivalents of appropriate base was stirred for the appropriate time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The mixture was diluted with dichloromethane (15 mL), washed with water (2x10 mL) and brine solution (2x10 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (n-hexane/ethyl acetate 3/1) to afford the corresponding N^5-acyl-1,2,5-thiadiazolidine 1,1-dioxides.

4.7. Conventional Procedure for *N*-Acylation of Cyclic Sulfamides with Carboxylic Acids (for products *3e, 3g, 3h*) [8].

To a stirred solution of carboxylic acid (1.5 mmol) in dry solvent (10 mL) was added HATU (2 mmol) followed by 3 mmol of appropriate base and non-*N*-substituted cyclic sulfamides (1.2 mmol) in the some solvent under a nitrogen atmosphere. The mixture was stirred at room temperature for the given time (see Table 3) and the solvent was evaporated under reduced pressure. The residue was diluted with ethylacetate (30 mL) and washed with 5% aqueous HCl (2x10 mL), 5% $NaHCO_3$ (2x10 mL) and brine (2x10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford crude product. The crude product was purified by column chromatography on silica gel eluted with (n-hexanes/ethyl acetate 3:1) to afford the corresponding *N*-acylated cyclic sulfamides.

4.8. Microwave-Assisted Procedure for *N*-Acylation of Cyclic Sulfamides.

A mixture of non-*N5*-substituted cyclic sulfamide (1 equiv, 1mmol), carboxylic acid anhydrides with 2 drops of conc H_2SO_4 or acyl chloride (2 equiv, 3 mmol) with 3 equivalents of appropriate base in dry organic solvent (2 mL) was irradiated in microwave oven (300 W, 110 °C) for a few minutes with stirring. After completion of the reaction, the solution was extracted with ethyl acetate (2x10 mL) and the organic layer was washed with aqueous $NaHCO_3$ (5%, 2x10 mL), brine (2x10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to provide the crude product. Flash chromatography on silica gel using ethyl acetate n-hexane (1:3) as the eluent afforded the desired *N5*-acylCyclic sulfamid ***2a-2m***.

4.9. Microwave-Assisted Solvent-Free Procedure for *N*-Acylation of Cyclic Sulfamides.

A mixture of non-*N5*-substituted Cyclic sulfamide (1 mmol), acid anhydrie (or acyl chloride) and 2 drops of conc H_2SO_4 (1,5 mmol) (or 3 equivalents of appropriate base) was placed in Teflon microwave vessels. The system was heated in a microwave oven at 300 W for a few minutes (monitored by TLC). On completion of the reaction, the mixture was extracted with ethyl acetate, washed with aqueous $NaHCO_3$ (5%, 2x10 mL), brine (2x10 mL) dried over anhydrous Na_2SO_4 and

solvent removed under reduced pressure. The crude product was purified by column chromatography over silica gel using ethyl acetate n-hexane (1:3) as the eluent.

[N^2-(2')-(propionic acid methyl ester), N^5-propionyl]-1,2,5-thiadiazolidine 1,1-dioxide (3f) [8]**.** Compound ***3f*** was prepared using ***1h*** (1 equiv, 1 mmol, 0.208 g). Compound ***3f*** was obtained as white solid in 74% yield by conventional heating, 93% yield by MWI in CH_3CN and 90% yield in the MWI solvent-free reaction. TLC: R_f=0.56 (CH_2Cl_2); m.p= 90-91°C; IR (KBr) ν cm-1: 1750-1715 (C=O), 1375 and 1160 (SO_2) ; ^{1}H-NMR ($CDCl_3$, δ ppm): 4.15 (q, *J*=7.8 Hz, 1H), 3.80 (t, *J*=6.2 Hz, 2H), 3.70 (s, 3H), 3.65 (t, *J*=6.7 Hz, 2H), 2.85 (q, *J*=7.4 Hz, 2H), 1.50 (d, 3H, *J*=7.8 Hz), 1.15 (t, 3H, *J*=7.4 Hz, 3H); LRMS (CI): 265 $[M+H]^+$.

N^2-Boc-4-isobutyl-N^5-(2-(3-methoxyphenyl)acetyl)-1,2,5-thiadiazolidine 1,1-dioxide (3g) [8]**. C**ompound ***3g*** was prepared using ***1d*** (1 equiv, 1 mmol, 0.278 g). Compound ***3g*** was obtained as an oil in 31% yield by conventional heating, 80% yield by MWI in toluene and 72% yield in the MWI solvent-free reaction. R_f = 0.57 (SiO_2, CH_2Cl_2); IR (KBr, ν cm^{-1}): 1749-1718 (C=O), 1374 and 1159 (SO_2); ^{1}H NMR ($CDCl_3$, δ ppm): 0.92 (t, 6H, $2CH_3$), 1.57 (m, 2H, CH_2), 1.58 (s, 9H, *t*Bu), 1.63 (m, 1H, CH), 3.78 (m, 2H, CH_2), 3.79 (s, 3H, O-CH_3), 4.03 (q, 2H, CH_2), 4.54 (m, 1H, CH); 6.80-7.22 (m, 4H, H-Ar); LRMS (CI): 427 $[M+H]^+$.

N^2-Boc-N^5-(2-(3-fluorophenyl)acetyl)-4-isobutyl-1,2,5-thiadiazolidine 1,1-dioxide (3h) [8]**. C**ompound ***3h*** was prepared using ***1d*** (1 equiv, 1 mmol, 0.278 g). Compound ***3h*** was obtained as an oil in 28% yield by conventional heating, 70% yield by MWI in CH_2Cl_2 and 67% yield in the MWI solvent-free reaction. TLC: R_f = 0.53 (SiO_2, CH_2Cl_2); IR (KBr, ν cm^{-1}): 1752-1720 (C=O), 1365 and 1150 (SO_2); ^{1}H NMR ($CDCl_3$, δ ppm): 0.92 (t, 6H, $2CH_3$), 1.57 (m, 2H, CH_2), 1.58 (s, 9H, *t*Bu), 1.63 (m, 1H, CH), 3.78 (m, 2H, CH_2), 4.02 (q, 2H, CH_2), 4.54 (m, 1H, CH), 6.90-7.30 (m, 4H, H-Ar); LRMS (CI): 415 $[M+H]^+$.

N^2-Boc-4-isobutyl-N^5-(3-phenylpropanoyl)-1,2,5-thiadiazolidine 1,1-dioxide (3l) [8]**. C**ompound ***3l*** was prepared using ***1d*** (1 equiv, 1 mmol, 0.278 g). Compound **3n** was obtained as an oil in 36% yield by conventional heating, 70% yield by MWI in toluene and 59% yield in the MWI solvent-free reaction. TLC: R_f = 0.49 (SiO_2, CH_2Cl_2); IR (KBr, ν cm^{-1}): 1747-1717 (C=O), 1380 and 1139 (SO_2); ^{1}H NMR ($CDCl_3$, δ ppm): 0.94 (d, 6H, $2CH_3$), 1.57 (m, 2H, CH_2), 1.58 (s, 9H, *t*Bu), 1.61 (m, 1H, CH), 2.98 (m, 3H, CH_aH_b), 3.10 (m, 1H, CH_aH_b), 3.73 (m, 2H, CH_2), 4.53 (m, 1H, CH); 7.20 (m, 5H, H-Ar); LRMS (CI): 411 $[M+H]^+$.

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