# Acid-catalyzed intramolecular cyclisation of *N*-(4,4-diethoxybutyl)sulfonamides as a novel approach to the 1-sulfonyl-2-arylpyrrolidines

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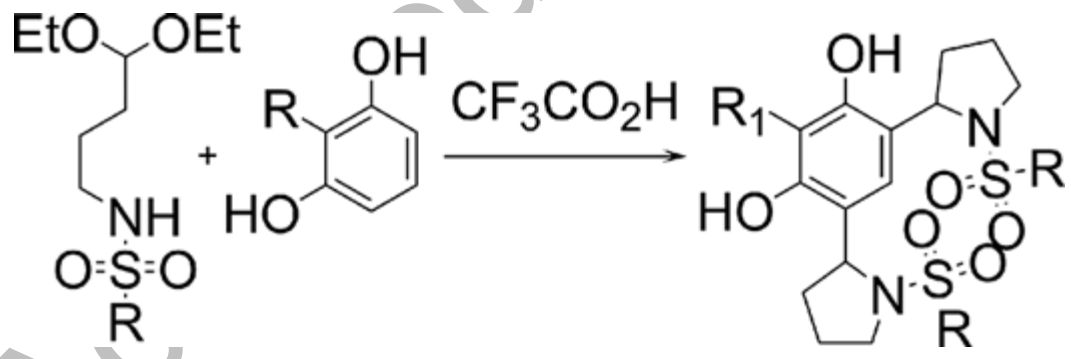
## Abstract

Herein we report our studies on the acid-catalyzed cyclisation of N-(4,4-diethoxybutyl)sulfonamides at the presence of polyatomic phenols as an efficient one-pot approach to the synthesis of 1-sulfonyl-2-arylpyrrolidines from the acyclic precursors.

**Graphical Abstract:**




**KEYWORDS:** acetal, cyclisation, resorcinol, pyrrolidine, sulfonamide

## INTRODUCTION

Pyrrolidine derivatives containing sulfonamide group and aromatic moiety exhibit wide range of biological activity. 1-Sulfonyl-2-arylpyrrolidines are suggested for the treatment of thromboembolic[1,2] and neurodegenerative disorders, such as Huntington, Parkinson[3,4] and Alzheimer[5] deseases. There is also evidence of the ability of these compounds to inhibit matrix metalloproteinase 2 (MMP2).[6]

The most widely used approach to the synthesis of these compounds is an intramolecular cyclisation of aryl substituted alkenes and alkynes containing sulfonamide group. A cyclisation of but-3-ene-1-amines,[7–16] but-3-yne-1-amines,[17] pent-4-ene-1-amines,[18–20] hexa-4,5-dien-1-amines[21,22] can be given as an example (Scheme 1).

The other methods include oxidative cyclisation of sulfonamides,[23–27] carbonylation of N-tosylpentenamine derivatives,[28,29] reaction of sulfonamides with cyclopropanes[30–32] and [3+2] cycloaddition of N-tosyl-4-aminobutanal with alkenes.[33] In general, these reactions require usage of metal catalysts, such as palladium salts,[10,11,14,15,28] rhodium[13,29] and gold[30–32] complexes; hypervalent iodine compounds are also used.[23–26] The most obvious way of the synthesis of 1-sulfonyl-2-arylpyrrolidines is a reaction of 2-arylpyrrolidines with sulfonyl chlorides,[4,6,34] which is, however, used only occasionally.

The common disadvantages of abovementioned methods are harsh reaction conditions, usage of expensive catalysts and reagents. The need in preliminary synthesis of

appropriately substituted starting compounds is also limits these approaches. Thus, the development of novel, effective method of synthesis of 1-sulphonyl-2-arylpyrrolidines is of great interest.

## DISCUSSION

Earlier, we have developed approach to the synthesis of 2-arylpyrrolidine-1-carboxamides based on trifluoroacetic acid-catalyzed intramolecular cyclisation of (4,4-diethoxybutyl)ureas at the presence of various phenols. Reaction proceeds in mild conditions and leads to the target compounds with good to high yields (Scheme 2).[35–38]

Since amide and sulfonamide groups are isosteric and possess similar electronic characteristics, we supposed that *N*-(4,4-diethoxybutyl)sulfonamides are also able to undergo intramolecular cyclisation in acidic media giving rise to 1-sulfonylpyrrolidines. This hypothesis was further supported by some papers describing formation of heterocyclic products in the reaction of 4,4-diethoxybutane-1-amine with arylsulfonyl chlorides.[39–41]

We attempted to synthesize starting *N*-(4,4-diethoxybutyl)-4-methylbenzenesulfonamide **1a** according to the previously described procedure[41] via the reaction of 4,4-diethoxybutane-1-amine with tosyl chloride at the presence of triethylamine. Surprisingly, the reaction product appeared to be not the target sulfonamide **1a**, but 2-ethoxypyrrolidine **2a** (Scheme 3), which was obtained with 58% yield. Further studies have shown that the result of this reaction depends on the order of mixing the reactants.

The slow addition of tosyl chloride to the solution of triethylamine and 4,4-diethoxybutane-1-amine leads to the formation of 2-ethoxypyrrolidine **2a**. When the order of mixing the reactants is reversed, i.e. 4,4-diethoxybutane-1-amine is added to the solution of tosyl chloride and triethylamine, the sulfonamide **1a** became a sole product. We assume that in this case the first stage of the reaction is the formation of sulfonamidinium salt[42] which subsequently undergoes nucleophilic substitution with elimination of triethylamine. Thus, we have found reaction conditions allowing selective preparation of either 2-ethoxypyrrolidine **2a** or its acyclic precursor **1a**. The arylsulfonamides **1b,c** and 2-ethoxy-1-(phenylsulfonyl)pyrrolidine **2b** were obtained in similar way.

These results were of a considerable interest both for the synthesis of key *N*-(4,4-diethoxybutyl)sulfonamides as well as intramolecular cyclization of these compounds. Therefore, we further studied the interaction of 4,4-diethoxybutan-1-amine with sulfonyl chlorides having alkyl substituent at sulfur atom. The product of the reaction of 4,4-diethoxybutan-1-amine with ethanesulfonyl chloride was found to be the *N*-(4,4-diethoxybutyl)methanesulfonylamide **1d** regardless of its conditions. It should be noted that the formation of the corresponding 2-ethoxy-1-methanesulfonilpirrolidines **2d** was detected by NMR spectroscopy. However, this compound easily undergo ring opening during reaction workup and we failed to isolate it. The mechanism of this ring opening probably similar to the mechanism described by us previously[36] for the pyrrolidine-1-carboxamides. Reaction of 4,4-diethoxybutan-1-amine with methanesulfonyl chloride proceeds similarly and leads to the formation of sulfonamide **1e** (Scheme 4).

Thus, we succeeded in the synthesis of starting *N*-(4,4-diethoxybutyl)sulphonamides having both aromatic and aliphatic substituent at sulfur atom. Moreover, results obtained during these studies suggest their easy cyclisation in acidic media with pyrrolidine core formation.

With this in hand, we started to study the reactions of *N*-(4,4-diethoxybutyl)sulphonamides with phenols. *N*-(4,4-Diethoxybutyl)-4-methylbenzenesulfonamide **1a** was taken as a model compound. Interaction of sulphonamide **1a** with resorcinol, 2-methylresorcinol and pyrogallol in chloroform at the presence of trifluoroacetic acid led to the formation of pyrrolidine derivatives **3a**, **4a** and **5a** (Scheme 5). All of these compounds were isolated as a mixtures of diastereomers, diastereomeric ratio was determined by $^1$H NMR spectroscopy (Table 1, № 1-3). Interestingly, carrying out these reactions in benzene allowed us to isolate pyrrolidines **4a** and **5a** as a single diastereomers (Table 1, №5,6). In case of compound **3a** the diastereomeric ratio was also improved significantly (Table 1, №4). However, reasons of such a significant effect of a solvent on a diastereomeric ratio are not clear enough at the moment.

Encouraged with these results, we examined the interaction of resorcinol, 2-methylresorcinol and pyrogallol with acetals **1c-e** in benzene (Scheme 6). Data obtained are summarized in Table 2.

Reaction of alkylsulfonamides **1d,e** with resorcinol, 2-methylresorcinol and pyrogallol led to the corresponding pyrrolidine derivatives **3-5** (Table 2, №10-15). The compounds **4d**,**e** were present in reaction mixture according to NMR data, however, we were not able to isolate them due to the gummy tar formation during reaction workup. All of the compound were obtained as single diastereomers. The arylsulfonamide **1c** reacted with phenols to form corresponding pyrrolidines **3c**-**5c**, but the reaction diastereoselectivity decreased significantly in this case (Table 2, №7-9).

We also were lucky enough to grow crystals of the compounds **3e**, **4a** and **5a,e** suitable for X-ray analysis. X-ray investigations of compounds **4a, 5e**, **3e** and **5a** revealed that all of them are crystal solvates with DMSO with different ratios (1 : 1 in **4a** and **5e**, 1 : 2 in **3e** and 1 : 3 in **5a**). The bond lengths, valence and torsion angles in molecules the studied compounds have values that are within standard for each type of chemical bond. Molecule of compound **3e** in crystal is in special position on the screw axe and have *R*,*R*-configuration. Molecules **4a, 5e**, and **5a** are in the general position and have *R*,*S*-configuration.

According to the literature data, 2-alkoxypyrrolidines are able to react with various nucleophiles, such as organosilicon compounds,[40,43–45] trialkylphosphites,[46] isocyanides[47] and trialkylbenzenes[48] at the presence of Lewis acids. In view of these data, we examined the interaction of 2-ethoxypyrrolidines **2** with phenols at the presence of trifluoroacetic acid (Scheme 7). The results are given in Table 3.

Expectedly, the reaction led to the formation of pyrrolidine derivatives **3**-**5**. Just as in the case of *N*-(4,4-diethoxybutyl)sulfonamides **1**, using chloroform as the solvent led to the formation of diastereomeric mixtures. Carrying out the same reactions in benzene allowed us to obtain target pyrrolidine derivatives **3b**-**5b** as a single diastereomers (Table 3, № 4-6).

Based on literature data, we proposed the following mechanism for these reactions (Scheme 8). The key step of the reaction is the elimination of ethanol molecule from the 2-ethoxypyrrolidine **2** leading to the formation of intermediate iminium ion **A**. Further reaction of this ion with aromatic nucleophile leads to the formation of target 2-arylpyrrolidines. In principle, these reactions can be considered as a variant of Mannich reaction, in which an N,O-acetal is used as an equivalent of carbonyl compound.[49,50]

In conclusion, we have developed a novel approach to the synthesis of 1-sulfonyl-2-arylpyrrolidines based on acid-catalyzed reaction of *N*-(4,4-diethoxybutyl)sulfonamides with phenols. The proposed approach benefits from simple one-step procedure, does not require the use of expensive reagents and catalysts and leads to the target compounds in good to high yields.

## EXPERIMENTAL

### Synthesis Of 1-Sulfonyl-2-Arylpyrrolidines, General Procedure A

To a solution of N-(4,4-diethoxybutyl)sulfonamide **1** (1.59 mmol) in chloroform (10 ml) appropriate phenol (0.80 mmol) and trifluoroacetic acid (1.59 mmol) were added.

Reaction mixture was stirred at room temperature for 12 h. Solvent was removed, the residue was washed with diethyl ether (10 ml) and dried in vacuum (r.t., 0.01 torr, 12 h).

**Synthesis Of 1-Sulfonyl-2-Arylpyrrolidines, General Procedure B**

To a solution of N-(4,4-diethoxybutyl)sulfonamide **1** (1.59 mmol) in benzene (10 ml) appropriate phenol (0.80 mmol) and trifluoroacetic acid (1.59 mmol) were added. Reaction mixture was stirred at room temperature for 12 h. Solvent was removed, the residue was washed with diethyl ether (10 ml) and dried in vacuum (r.t., 0.01 torr, 12 h).

**Synthesis Of 1-Sulfonyl-2-Arylpyrrolidines, General Procedure C**

To a solution of 2-ethoxypyrrolidine **2** (1.86 mmol) in chloroform (10 ml) appropriate phenol (0.93 mmol) and trifluoroacetic acid (1.86 mmol) were added. Reaction mixture was stirred at room temperature for 12 h. Solvent was removed, the residue was washed with diethyl ether (10 ml) and dried in vacuum (r.t., 0.01 torr, 12 h).

**Synthesis Of 1-Sulfonyl-2-Arylpyrrolidines, General Procedure D**

To a solution of 2-ethoxypyrrolidine **2** (1.86 mmol) in benzene (10 ml) appropriate phenol (0.93 mmol) and trifluoroacetic acid (1.86 mmol) were added. Reaction mixture was stirred at room temperature for 12 h. Solvent was removed, the residue was washed with diethyl ether (10 ml) and dried in vacuum (r.t., 0.01 torr, 12 h).

## SUPPORTING INFORMATION

Full experimental procedures, characterization data and copies of NMR spectra for all synthesized compounds. This material can be found via the ‘‘Supplementary Content’’ section of this article’s webpage. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1479990- 1479993. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).


## ACKNOWLEDGMENT

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**Table 1.** Influence of solvent on diastereomeric ratio of pyrrolidines **3a-5a**.

| № | Cmpd | R | Solvent | *dr*[a] | Yield,[b] % |
|---|---|---|---|---|---|
| 1 | **3a** | H | $CHCl_3$ | 40 : 60 | 47 |
| 2 | **4a** | Me | $CHCl_3$ | 89 : 11 | 63 |
| 3 | **5a** | OH | $CHCl_3$ | 34 : 66 | 80 |
| 4 | **3a** | H | $C_6H_6$ | 87 : 13 | 33 |
| 5 | **4a** | Me | $C_6H_6$ | <95 : 5 | 77 |
| 6 | **5a** | OH | $C_6H_6$ | <95 : 5 | 48 |

[a]According to $^1$H NMR data

[b]Isolated yield

**Table 2.** Synthesis of pyrrolidines **3-5**.

| № | Compound | $R_1$ | $R_2$ | *dr*[a] | Yield,[b] % |
|---|---|---|---|---|---|
| 7 | **3c** | H | *p*-AcNH-$C_6H_4$ | 50 : 50 | 33 |
| 8 | **4c** | Me | *p*-AcNH-$C_6H_4$ | 34 : 66 | 28 |
| 9 | **5c** | OH | *p*-AcNH-$C_6H_4$ | 14 : 86 | 28 |
| 10 | **3d** | H | Et | <95 : 5 | 73 |
| 11 | **4d** | Me | Et | – | 0[c] |
| 12 | **5d** | OH | Et | <95 : 5 | 42 |
| 13 | **3e** | H | Me | <95 : 5 | 46 |
| 14 | **4e** | Me | Me | – | 0[c] |
| 15 | **5e** | OH | Me | <95 : 5 | 61 |

[a]According to $^1$H NMR data

[b]Isolated yield

[c]Compound was not isolated from byproducts

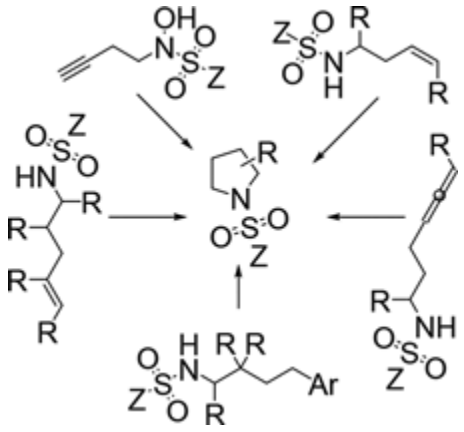
**Table 3.** Reaction of 2-ethoxypyrrolidines **2** with phenols.

| № | Compound | $R_1$ | $R_2$ | Solvent | *dr*[a] | Yield,[b] % |
|---|---|---|---|---|---|---|
| 1 | **3a** | *p*-Me-$C_6H_4$ | H | $CHCl_3$ | 50 : 50 | 80 |
| 2 | **4a** | *p*-Me-$C_6H_4$ | Me | $CHCl_3$ | 42 : 58 | 93 |
| 3 | **5a** | *p*-Me-$C_6H_4$ | OH | $CHCl_3$ | 50 : 50 | 64 |
| 4 | **3b** | Ph | H | $C_6H_6$ | <95 : 5 | 23 |
| 5 | **4b** | Ph | Me | $C_6H_6$ | <95 : 5 | 56 |
| 6 | **5b** | Ph | OH | $C_6H_6$ | <95 : 5 | 32 |

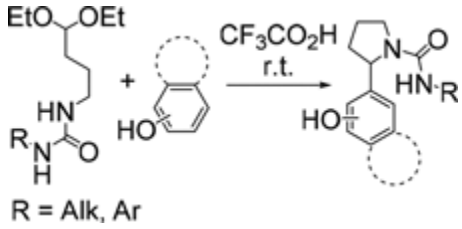
[a]According to $^1$H NMR data

[b]Isolated yield

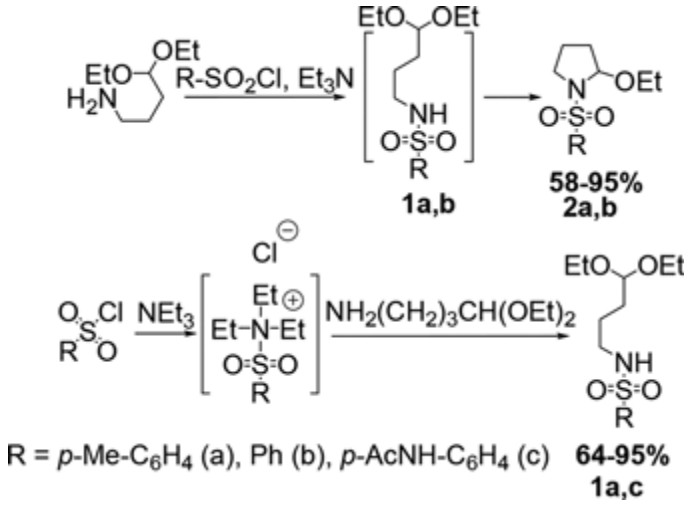
**Scheme 1.** The most widely used approaches to the 1-sulfonylpyrrolidines



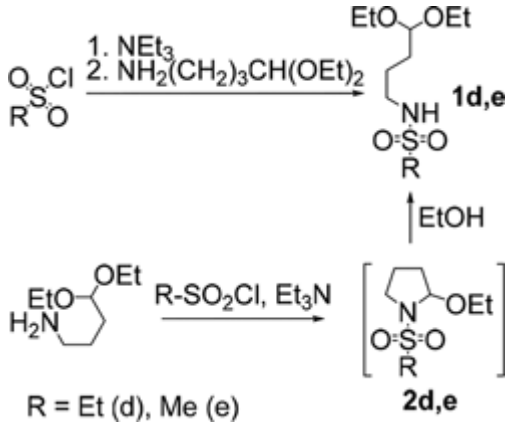
**Scheme 2.** Synthesis of 2-arylpyrrolidine-1-carboxamides.



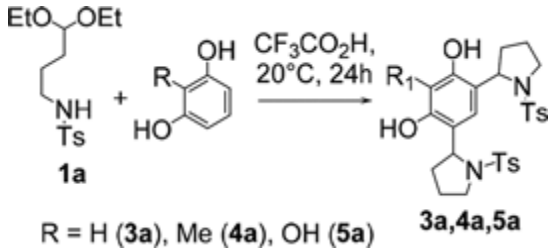
**Scheme 3.** Synthesis of arylsulfonamides **1a,c** and 2-ethoxypyrrolidines **2**.



**Scheme 4.** Synthesis of alkylsulfonamides **1d,e**.

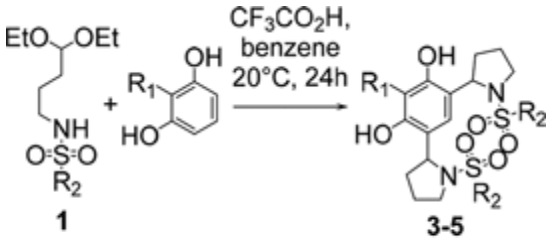


**Scheme 5.** Reaction of sulfonamide **1a** with phenols.




R = H (**3a**), Me (**4a**), OH (**5a**)

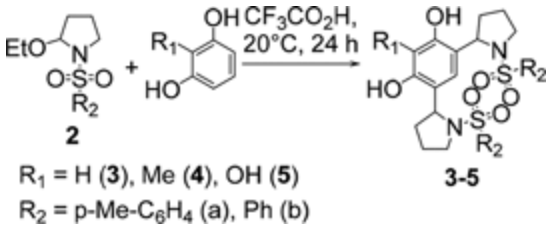
**Scheme 6.** Reaction of phenols with sulfonamides **1c-e**.




$R_1$ = H (**3**), Me (**4**), OH (**5**)

$R_2$ = *p*-AcNH-$C_6H_4$ (c), Et (d), Me (e)

**Scheme 7.** Reaction of 2-ethoxypyrrolidines **2** with phenols.




$R_1$ = H (**3**), Me (**4**), OH (**5**)
$R_2$ = p-Me-$C_6H_4$ (a), Ph (b)

**Scheme 8.** Proposed mechanism for the 2-arylpyrrolidines formation.

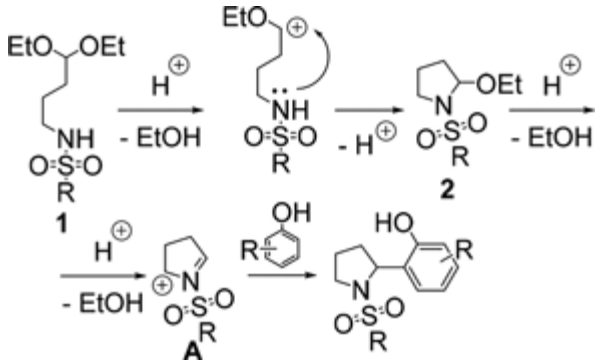


**Figure 1.** Molecular structure of *R*,*R*-**3e** and *R*,*S*-**5e** in studied crystals. H-atoms are omitted for clarity.