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An efficient synthesis of sulfamides

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ABSTRACT

Here we report an efficient synthesis of sulfamides. 3,5-Lutidine was found to be an optimal solvent and catalyst for the reaction. The method was developed during our efforts to synthesize a series of novel FKBP-12 inhibitors in which the known ketoamide linker was replaced with sulfamide.

The sulfamide functional group ($R_2NSO_2NR_2$)[1] can be found in a number of marketed and investigational drugs intended to treat a wide variety of conditions, examples of which are shown in Table 1. In recent years, molecules containing sulfamides have also been investigated as inhibitors of ATP-sensitive potassium channels,[2] carbonic anhydrase,[3] carboxypeptidase A,[4] γ-secretase,[5] glycosidase,[6] HCV polymerase (NS5B),[7] HIV-1 integrase,[8] HIV-1 protease,[9] histone deacetylase,[10] human chymase,[11] human leukocyte elastase,[12] kinesin spindle protein,[13] monoamine reuptake,[14] plasma cell membrane protein-1,[15] and thrombin;[16] as agonists of androgen receptor,[17] β_3-andrenergic receptor,[18] and PPAR;[19] and as antagonists of CXCR2.[20]

The widespread pharmaceutical use of sulfamides may be attributed to their unique chemical and structural features, as well as their ability to confer desirable physical properties. A tetrahedral sulfur atom and multiple vectors for substitution off the nitrogen atoms lead to conformational and structural diversity. Depending on the degree of substitution, the number of hydrogen-bond donors and acceptors can be varied, and the lipophilicity tuned. Sulfamides can be used as a bioisosteres of amides, ureas, carbamates, ketoamides, esters, sulfonamides, or sulfamates. Like ureas, sulfamides may be less prone to acidic, basic, or enzyme-catalyzed hydrolysis than other isosteres. Compared to the more commonly used sulfonamide, the extra nitrogen of the sulfamide provides more hydrogen-bonding potential, as well as different physical properties such as log *P* and solubility.

Primary sulfamides ($R^1R^2NSO_2NH_2$) can be made from sulfamide itself, either by heating with an amine[23] or by reductive amination of an aldehyde.[21] Amines can also be acylated by unsubstituted sulfamoyl chloride, which is often generated in situ by the reaction of chlorosulfonyl isocyanate with formic acid[16] or water.[13] BOC- or CBZ-protected sulfamoyl chlorides can be generated in situ by the reaction of chlorosulfonyl isocyanate with *tert*-butyl alcohol[24,10] or benzyl alcohol,[4] allowing selective further functionalization, though these reagents are somewhat unstable. The more stable *N*-(*tert*-butoxycarbonyl)-*N*-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]azanide[24] is also employed in the synthesis of BOC-protected primary sulfamides.

Sulfamides with a higher degree of substitution are commonly synthesized by the reaction of a substituted sulfamoyl chloride with an amine in the presence of a base such as triethyl amine or pyridine.[8,18,23] Sterically hindered or less reactive amines, however, may be sluggish to these conditions, leading to side products and decomposition of the sulfamoyl chloride. Activating/stabilizing groups such as oxazolidinone[25] and imidazolium triflates[26,19] have been employed to improve the efficiency of difficult reactions. This Letter describes a difficult sulfamide synthesis we encountered, and how mechanistic investigation of the side product led to our use of 3,5-lutidine as a novel solvent/base/activating group.

In our neuroimmunophilin project, we sought to design and synthesize novel FKBP (FK506 Binding Protein) inhibitors with better metabolic stability and physical properties. As a substitute for a potentially reactive and metabolically unstable ketoamide, a sulfamide linker was proposed. The sulfamides with a general structure **11a/b** shown in Scheme 1 were targets of synthetic efforts. The amine core (**8a/b**) can be readily synthesized in 2–3 steps. The alkyl esters (**7a/b**) of proline and pipecolinic acid were prepared from *N*-CBz amino acids (**6a/b**). The CBz group was removed under standard hydrogenation conditions to give the free amines (**8a/b**).

To form the sulfamide moiety, several known protocols for sulfamoyl chloride formation were tested. At room temperature, the mixture of sulfuryl chloride and the amine (**8a/b**) showed no reaction even with addition of Lewis acids. Higher temperatures only led to decomposition. The more reactive thionyl chloride was proposed as a substitute for sulfuryl chloride, though the products would require oxidation at a later stage. Unfortunately, the addition of amines (NH_2R) to thionyl chloride gave a complex mixture. Next we decided to test sulfamide formation via substituted sulfamoyl chloride prepared from the amine (**8a/b**). The amine (**8a/b**) was treated with chlorosulfonic acid and triethyl-

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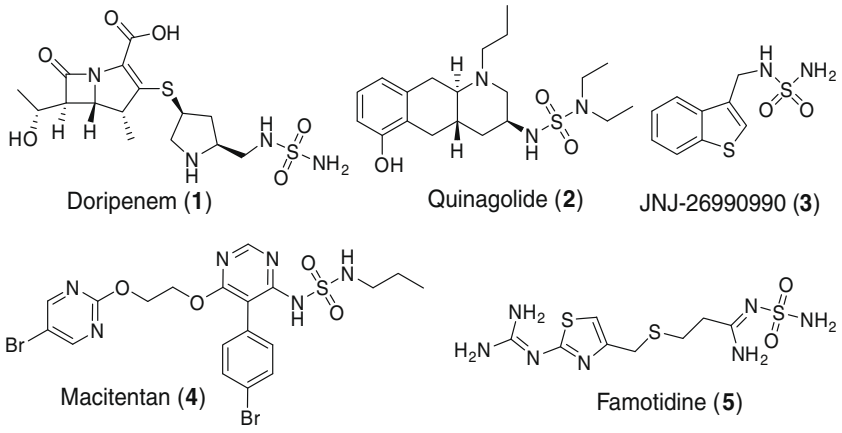
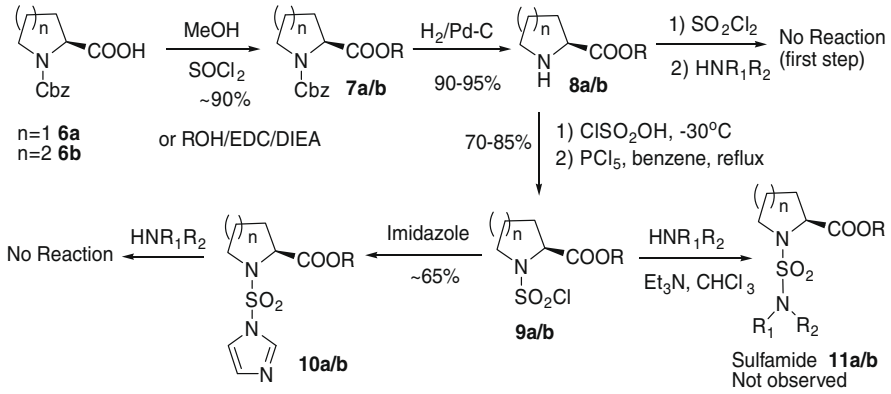
Table 1
Examples of sulfamide-containing drugs

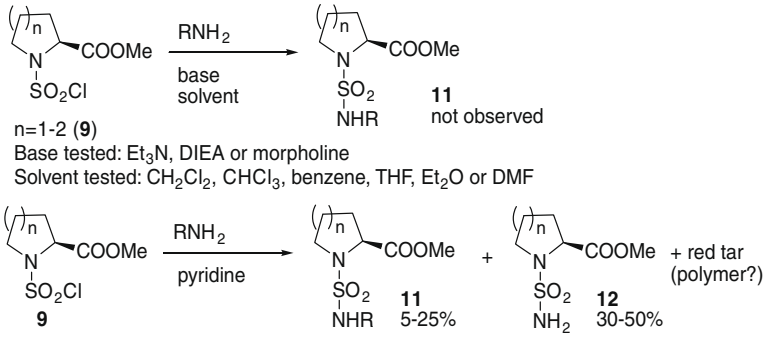


Compound	Indication	Stage	Company
Doripenem (**1**)	Broad-spectrum antibiotic	On market	Shinogi/Johnson & Johnson
Quinagolide (**2**)	Hyperprolactinaemia	Marketed outside US/Japan	Ferring Pharmaceuticals
JNJ-26990990 (**3**)	Broad-spectrum Anticonvulsant	Ph I[21]	Johnson & Johnson
Macitentan (**4**)	Pulmonary arterial hypertension	Ph III[22]	Actelion
Famotidine (**5**)	Gastroesophageal reflux disease	On market	Johnson & Johnson/Merck

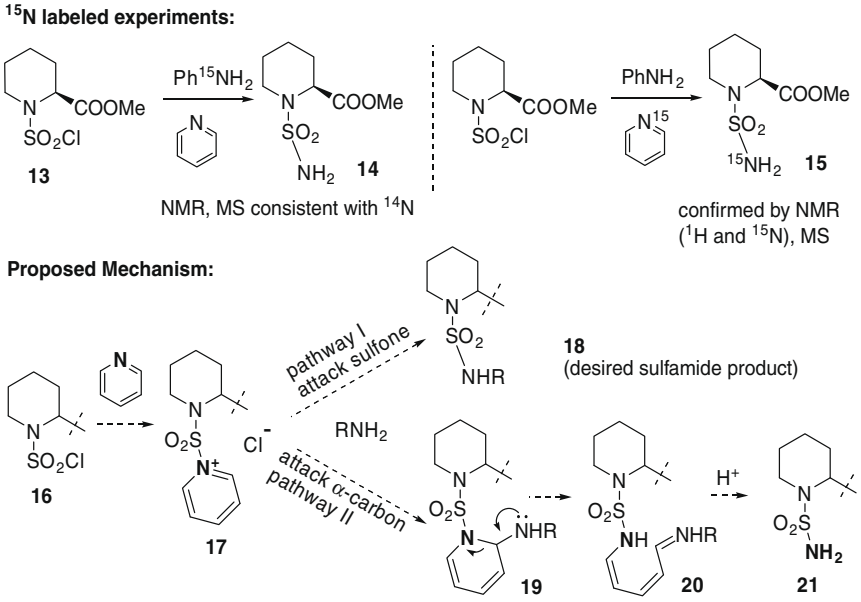


Scheme 1.

amine at −30 °C to give a sulfamoic acid, which was heated with phosphorous pentachloride to give the sulfamoyl chloride (**9a/b**) in good isolated yield (50–90%).[27] However, our attempts to displace the chlorine of the sulfamoyl chloride (**9a/b**) by amines in the presence of triethylamine gave none of the desired sulfamide (**11a/b**). At low temperature (−78 °C to −30 °C) as suggested in the literature, no reaction was observed. Heating at ambient or higher temperatures (25–50 °C) resulted in decomposition. To increase stability, the sulfamoyl chloride was converted to sulfamoyl imidazole (**10a/b**), but this intermediate was not reactive toward amines, even with large excess of the amines and at a higher temperature (70 °C).

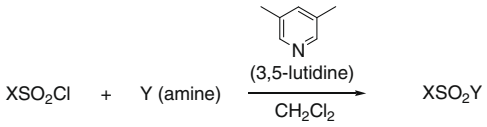


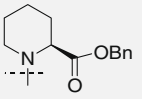
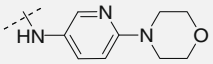
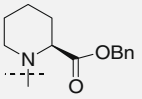
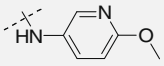
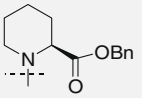
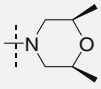
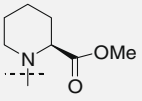
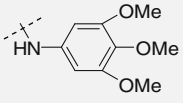
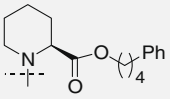
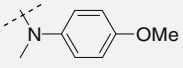
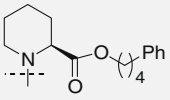
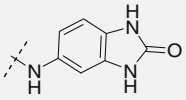
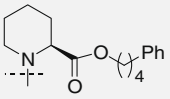
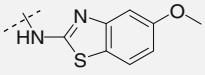
Scheme 2.



Scheme 3.

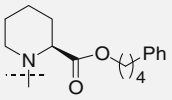
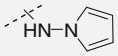
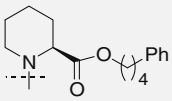
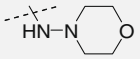
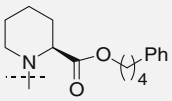
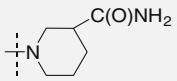
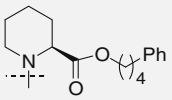
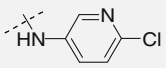
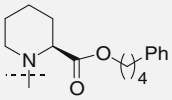
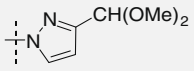
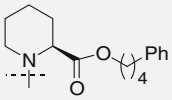
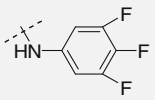
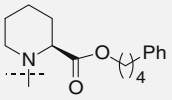
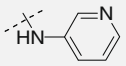
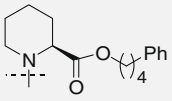
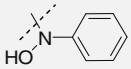
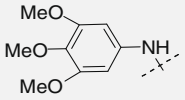
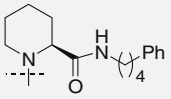
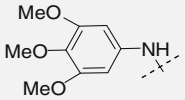
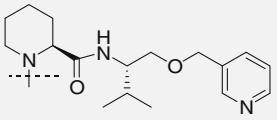
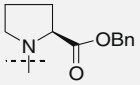
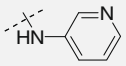
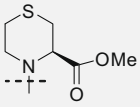
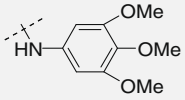
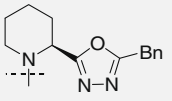
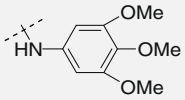
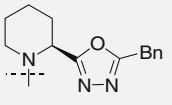
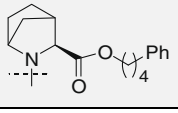
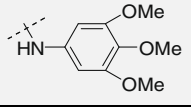
Table 2
Sulfamides prepared by following above-mentioned general procedure



Compound	X	Y	Isolated yield (%)
22			72
23			89
24			99
25			88
26			95
27			70
28			2

(*continued on next page*)

Table 2 (*continued*)

Compound	X	Y	Isolated yield (%)
29			90
30			15
31			75
32			96
33			94 (10:1 regioisomers)
34			46
35			69
36			55
37			25
38			67
39			99
40			83
41			87
42			45
43			75

To investigate the reaction between the sulfamoyl chloride (**9a/b**) and the amines, we screened a number of solvent (CH_2Cl_2, $CHCl_3$, benzene, THF, Et_2O, DMF) and base (Et_3N, DIEA, morpholine) combinations (Scheme 2), but found that only pyridine as both

solvent and base gave the desired product sulfamides (**11**) although in a very low yield (5–25%). A detailed characterization of the side products in the reaction mixture revealed that the primary sulfamide (**12**) was the main product formed (50–60%). The finding is surprising because there is no ammonia or its equivalent in the reaction.

To identify the source of the terminal NH_2 and to understand the mechanism that produced this side product (**12**), ^{15}N-labeled aniline and ^{15}N-labeled pyridine were used in two different runs of this reaction (Scheme 3). When ^{15}N-labeled aniline was used, the primary sulfamide (**14**) was isolated without measurable enrichment of ^{15}N.[28] With ^{15}N-labeled pyridine as a solvent, ^{15}N-labeled **15** was isolated.[29] These results suggested that the terminal NH_2 of **12** came from pyridine. We propose a reaction mechanism (Scheme 3) in which the sulfamoyl chloride is first activated by the formation of pyridinium salt. Nucleophilic addition of aniline to the sulfone, with pyridine as a leaving group, leads to the desired sulfamide product **18.** Alternatively, nucleophilic attack of the aniline on the activated *ortho* or *para* positions of the pyridinium ring,[30] followed by ring opening hydrolysis results in the undesired primary sulfamide side product **21**. Based on the observed product ratio, pathway II is favored under our reaction conditions.

According to the proposed mechanism, pyridine plays three key roles in the reaction—(1) co-solvent with a favorable dipole environment; (2) catalyst to activate the sulfamoyl chloride; (3) base. To facilitate the formation of desired sulfamide via pathway I, lutidines were substituted for pyridine as base/co-solvent. The steric bulk of the extra methyl groups might impede nucleophilic addition to the pyridinium ring, thus disfavoring pathway II. The reaction in 2,6-lutidine was found to be sluggish. Almost 95% of the sulfamoyl chloride remained even after 24 h. The basic nitrogen of 2,6-lutidine may be too hindered to activate the sulfonyl chloride via formation of a pyridinium salt, which seems to be critical for the reaction. On the other hand, the reaction was faster and cleaner with 3,5-lutidine as the base, affording the desired sulfamide in a substantially improved yield (up to 90% yield). Only a minimal amount (<5%) of the primary sulfamide side product was observed. 3,5-Lutidine not only provides the desirable dipole environment, base, and catalytic effect of pyridine but also minimizes the formation of the undesired side product by slowing down nucleophilic addition of the amine to the pyridinium ring. Using 3,5-lutidine as the solvent/base, a large number of sulfamides with diverse structures were prepared, as shown in Table 2.[31]

Typical conditions for sulfamide formation: To a 3,5-lutidine solution (1 mL) of 3,4,5-trimethoxyaniline (176 mg, 0.96 mmol) was added (*S*)-methyl 1-(chlorosulfonyl)piperidine-2-carboxylate (compound **25X**, 116 mg, 0.481 mmol) in CH_2Cl_2 (1 mL) at 25 °C. After 20 hours, the mixture was diluted with EtOAc (40 mL) and washed with 5% HCl solution (ice-cold, 25 mL) and brine (25 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (25–30% EtOAc in hexanes) to provide 165 mg (88%) of sulfamide **25** as a white solid.

In summary, new sulfamide formation conditions have been established by studying the mechanism of the side product formation. As a result, we were able to synthesize a new class of FKBP inhibitors. The new sulfamide formation protocol provides medicinal chemists an additional effective method for synthesizing sulfamides, which potentially have more favorable pharmaceutical properties.

Supplementary data

Supplementary data (analytical data (spectroscopic and physical characterization) for new sulfamides reported in this work is included as Supplementary data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.106.

References and notes

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28. Compound **14** was found to have a parent MS ion [MS($M+H^+$): 223] and ^1H NMR (broad singlet on peak for NH_2 in deuterated DMSO) consistent with unlabeled product.
29. Compound **15** was found to have a parent MS ion [MS($M+H^+$): 224], ^1H NMR (doublet peak for NH_2 in deuterated DMSO) and ^{15}N NMR (triplet peak for NH_2) consistent with ^{15}N-labeled product.
30. Nucleophilic addition to either *ortho* or *para* position of the pyridinium ring can lead to the same terminal sulfamide side product (**21**). *Ortho* addition is shown as an example in the proposed mechanism.
31. Synthetic procedure and analytical data of all compounds listed herein have been previously reported in following patent publication. Guo, C.; Dong, L.; Hou, X.; Vanderpool, D. L.; Villafranca, J. E. PCT Int. Appl. WO 01/40185 A1, 2001.