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Synthesis and structural study of *N*-acetyl-1,2,3,4-tetrahydroisoquinoline-2-sulfonamide obtained using $H_6P_2W_{18}O_{62}$ as acidic solid catalyst

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HIGHLIGHTS

- Best yields for acylation of sulfamides are obtained in acetonitrile with $H_6P_2W_{18}O_{62}$ as acidic solid catalyst.
- Structural studies of sulfamides, before and after acylation, are achieved and compared.
- Intermolecular interactions are highlighted in the two compounds with the help of Hirshfeld surfaces.
- The two crystal structures present a similar sandwich supramolecular organization.

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ABSTRACT

At room temperature and under acidic conditions, acylation of sulfamides derivatives in various solvents using diverse solid catalysts has been investigated. The best yields are obtained in acetonitrile with a Wells–Dawson type heteropolyacid $H_6P_2W_{18}O_{62}$ as acidic solid catalyst. Crystals of *N*-acetyl-1,2,3,4-tetrahydroisoquinoline-2-sulfonamide suitable for X-ray study have been obtained after recrystallization in toluene. The detailed analysis of molecular and crystal structure is presented in comparison with the structure of 1,2,3,4-tetrahydroisoquinoline-2-sulfonamide, before acylation, previously studied by our team. The role of both intra- and intermolecular weak interactions is discussed. The Hirshfeld surfaces analysis in form of d_{norm} representation and decomposed fingerprint plots were used to find out different weak but directional hydrogen bonds and π interactions. Both structures present similar sandwich structures with alternation of primary layers involving strong hydrogen bonds with secondary layers involving mostly weaker interactions.

1. Introduction

Within the realm of proven pharmacophores, the sulfamide functional group (thiadiazine-1,1-dioxide) stands out as one of the most important structural motifs found in high affinity protein ligands and pharmaceutically useful agents. Sulfamide is a quite simple molecule incorporating the sulfonamide functionality **1** widely used by medicinal chemists for the design of a host of biologically active derivatives with pharmacological applications, since the 1940s [1]. Some of sulfamide compounds have proven to be particularly effective as inhibitors of key enzymes including HIV protease [2], serine protease [3], carbonic anhydrase [4] and matrix metalloproteinase [5]. Beyond their clear significance in the treatment of disease, sulfamides constitute an increasingly popular set of building blocks within the field of supramolecular chemistry [6].

Attachment of an acyl group to the sulfamide group **2** gives the more acidic acyl sulfamide **3** (Scheme 1). The most common methods for the *N*-acylation of sulfonamides are the reaction of parent sulfonamides with acyl chlorides or anhydrides in the presence of trialkyl amines, pyridine [7], H_2SO_4 [8], Lewis acids [9] or heterogeneous solid acid [10]. Other methods involve direct coupling of sulfamides with carboxylic acids using condensing agents such as carbodiimides (EDC or DCC) [11], *N*,*N*′-carbonyldiimidazole [12] or *N*-acylbenzotriazoles [13]. However, most of these procedures have significant drawbacks such as long reaction times, low yields, harsh reaction conditions, tedious workup procedures, or use of environmentally toxic reagents or media.

In recent years, the use of heterogeneous catalysts has received considerable interest in various disciplines including organic

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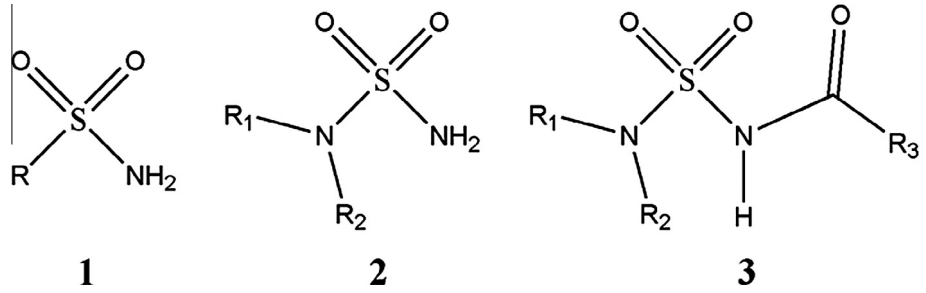
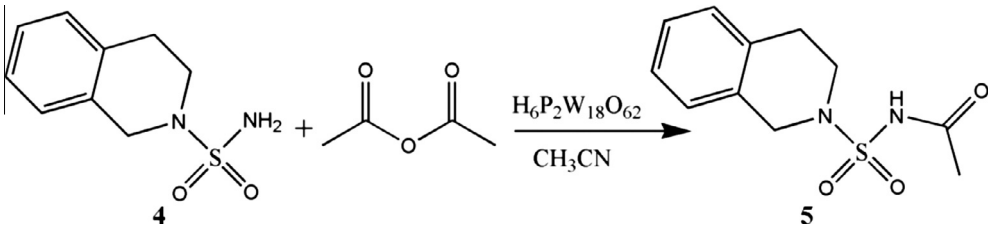


Scheme 1. Sulfonamide **1**, sulfamide **2** and *N*-acyl sulfamide **3** functional groups.



Scheme 2. *N*-acylation of the 1,2,3,4-tetrahydroisoquinoline-2-sulfonamide **4** with acetic anhydride using $H_6P_2W_{18}O_{62}$ as catalyst.

Table 1
N-acylation of 1,2,3,4-tetrahydroisoquinoline-2-sulfonamide **4** with acetic anhydride in different solvents using $H_6P_2W_{18}O_{62}$ (1 mmol%) catalyst.

Solvent	Time (min)	Conversion (%)
Toluene	30	80
$CHCl_3$	60	65
THF	60	55
CH_2Cl_2	60	62
CH_3CN	15	95

Table 2
Catalytic effect of $H_6P_2W_{18}O_{62}$ in the *N*-acylation of **4** with acetic anhydride.

$H_6P_2W_{18}O_{62}$ (mmol%)	Time (min)	Conversion (%)[a]
0.25	60	50
0.5	30	91
1	15	95
1.25	15	95

[a] The conversion was determined by ^1H NMR analysis of the crude product.

synthesis owing to their easy work-up procedures, easy filtration, and minimization of cost and waste generation due to reuse and recycling of these catalysts [14]. Heteropolyacids have many advantages finding economically and environmentally attractive in both academic and industrial significance; they are useful acids and oxidation catalysts in various reactions since their catalytic features can be varied at a molecular level [15]. Many typical acid-catalyzed reactions, including acylation of sulfamides [16], are all effective in the presence of a suitable Wells–Dawson type heteropolyacid catalyst.

First of all, herein are described the results of our investigation of acylation of sulfamides derivatives in various solvents using diverse solid catalysts. Then, the synthesis and characterization of *N*-acetyl-1,2,3,4-tetrahydroisoquinoline-2-sulfonamide **5**, obtained as investigating *N*-acylation of the 1,2,3,4-tetrahydroisoquinoline-2-sulfonamide **4** by a Wells–Dawson type heteropolyacid $H_6P_2W_{18}O_{62}$ as acidic solid catalyst (Scheme 2) are detailed. Finally, suitable crystals of **5** for X-ray data collection have been obtained. The corresponding crystal structure **I** is described. Intra- and intermolecular interactions in this crystal structure are analysed in comparison with the structure of 1,2,3,4-tetrahydroisoquinoline-2-sulfonamide **4** [17]. Non-covalent molecular interactions, including hydrogen bonds, aromatic π-stackings and even weaker interactions, such as C—H···O and C—H···π, can all be decisive in controlling the molecular assembly in organic compounds [18]. It is becoming fundamental to study the respective roles of all these non-bonded interactions in the packing organization. Patterns of close intermolecular interactions in the two crystal structures are highlighted with the help of Hirshfeld surfaces and 2D-fingerprint plots [19–21].

2. Experimental

2.1. Synthesis

2.1.1. Screening investigation of acylation of the 1,2,3,4-tetrahydroisoquinolin-2-sulfonamide *4* under acidic conditions at room temperature

The 1,2,3,4-tetrahydroisoquinolin-2-sulfonamide **4** was readily synthesized as described previously starting from chlorosulfonyl isocyanate for its reactive sulfamoyl group [17,22]. Due to this compound's lack of stability in basic reaction conditions, we have studied its *N*-acylation with acetic anhydride under acidic conditions at room temperature. An initial screen was conducted using $H_6P_2W_{18}O_{62}$ as catalyst in different aprotic solvents to find the best conditions (Table 1). The use of acetonitrile resulted in a highly efficient transformation (95%).

Furthermore, in order to test the catalytic activity of $H_6P_2W_{18}O_{62}$, this acylation was first optimized with amount of catalyst. It was found that the application of less than 1 mmol% of $H_6P_2W_{18}O_{62}$ gave a moderate conversion of the corresponding acyl sulfamide, whereas the use of more than 1 mmol% gave excellent conversion (Table 2).

Furthermore, we compared the catalytic activity of different catalysts. Without any catalyst, no product was observed even after prolonged reaction time. Comparison of catalysts montmorrillonite k10, H_2SO_4, $ZnCl_2$, $K_6P_2W_{18}O_{62}$, $H_3PW_{12}O_{40}$ and $H_6P_2W_{18}O_{62}$ (Table 3) showed that the activity was higher for