CONVENIENT SYNTHESIS OF NOVEL N-ACYLSULFONAMIDES CONTAINING PHOSPHONATE MOIETY

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INTRODUCTION

N-acylsulfonamides derivatives are well-known pharmaceutical agents since this group has been the main functional part of most of the drug structures due to stability and tolerance in human beings. These molecules have gained much attention due to their diverse biological activities in pharmaceutical as antibacterial inhibitors of tRNA synthetases,1 antagonists for Angiotensin II2 and Leukotriene D4-receptors.3 New N-acylsulfonamides were described such as 1 (Figure 1); these compounds are the prodrugs of celecoxib4 nonsteroidal, antiinflammatory, and selective COX-2 inhibitor used in the treatment of osteoarthritis and rheumatoid arthritis. Compound 2 (Figure 1), which is a prodrug of valdecoxib5 that is marketed for the hospital treatment of postoperative pain, also exemplifies this principle.

On the other hand, phosphonates have a variety of biological activities and may act as antibiotics and antiviral agents as well as insecticides and herbicides.6,7 The phosphonate functionality has been incorporated into a range of clinically useful drugs. In addition, acyclic nucleoside phosphonates have shown potential as therapeutics for pathogenic
species. For example, Tenofovir disoproxil fumarate (PMPA) is an approved agent for the treatment of HIV in humans, and has shown efficacy in the treatment of hepatitis B (HBV).\textsuperscript{8} The phosphonate moiety is also found in HIV protease inhibitors showing an enhanced resistance profile compared to that of the nonphosphonylated parent compounds.\textsuperscript{9} Phosphonate containing protease inhibitors also have shown great potential for the treatment of Hepatitis C virus.\textsuperscript{10} Alafosfalin—an antibiotic with a broad spectrum of activity—has been developed and demonstrates the ability to inhibit cell wall biosynthesis.\textsuperscript{11} It has proved to be potentially useful in the treatment of gastroenteritis and bacterial urinary tract infections.\textsuperscript{12}

Introduction of phosphonate esters into a molecule intended as a possible drug candidate enhances the water solubility, which changes its bioavailability. Such organophosphorus compounds have found practical application in medicine,\textsuperscript{13} agriculture,\textsuperscript{14} industry,\textsuperscript{15} and organic synthesis.\textsuperscript{16} In the literature, novel phosphonates containing sulfonamide moiety have been described and have interesting biological properties. New phosphonosulfonamides were described such as compound 3, which is used in the treatment of HIV protease,\textsuperscript{17} and compound 4, which was discovered to be potent inhibitor of protein tyrosine phosphatase 1B\textsuperscript{18} (Figure 2).

Several methods have been utilized by our group\textsuperscript{20,21} for the synthesis of phosphonate esters 5–7 (Figure 3), most notably the Michaelis–Arbuzov reaction.

Here we describe the synthesis of a new series of modified N-acylsulfonamides containing phosphonate moiety starting from chlorosulfonyl isocyanate (CSI), primary amines, and trimethylphosphite.

![Figure 1](image1.png)  
**Figure 1** Some drugs with N-acylsulfonamide functionality.

![Figure 2](image2.png)  
**Figure 2** Examples of phosphonates containing sulfonamide group.
RESULTS AND DISCUSSION

There are several approaches toward the synthesis of phosphonates, which focus on the formation of the crucial C–P bond. Of these methods, the Abramov, Pudovik, Michaelis–Becker, and Michaelis–Arbuzov (commonly called the “Arbuzov Reaction”) are the most well studied and documented.\(^{22}\) A search of the literature shows that the Arbuzov reaction is commonly used to form phosphonates, and in fact is the most common method of phosphorylation employed.\(^{23}\) The general method, which is employed to prepare the final compounds, is outlined in Scheme 1. The \(N\)-acylsulfonamides presented here were obtained in four steps by a simple and efficient methodology described below.

Scheme 1  Synthesis of novel \(N\) = Acylsulfonamides containing phosphonate moiety.
The sulfonamides\textsuperscript{24} (8a–f) were prepared by reaction of \textit{tert}-butanol and CSI in anhydrous methylene chloride at 0°C. After 30 min, the \(N\)-chlorosulfonyl carbamate and triethylamine were added to a solution of the primary amine in the same solvent. After completion of the reaction, the mixture was washed with 0.1 N HCl and then with water. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo to give sulfonamides 8a–f as white powders in excellent yields. The deprotection reaction of sulfonamides 8a–f was carried out in distilled water at 100°C for 30–60 min to give sulfonamides 9a–f in quantitative yields. The preparation of the \(N\)-acylsulfonamides 10a–f includes the reaction of sulfonamides 9a–f with chloroacetyl chloride in toluene in the presence of a Lewis acid catalyst at 110°C for 3 h.

Phosphorylation of \(N\)-acylsulfonamides 10a–f was easily achieved by Arbuzov reaction in the presence of a large excess of trimethylphosphate under reflux conditions.

In this study, we obtained some new \(N\)-acylsulfonamides containing phosphonate moiety in good to moderate yield. The structures of the synthesized compounds are confirmed by elemental analysis as well as by IR and \(^1\)H, \(^{13}\)C, and \(^{31}\)P NMR spectral data.

**CONCLUSION**

In conclusion, a series of \(N\)-(aryl or alkyl)-(1-(2-dimethoxyphosphoryl) acetamide) sulfamides 4a–f was synthesized with satisfactory yields. This synthesis has been performed easily starting from the corresponding \(N\)-(aryl or alkyl) sulfamoyl-2-chloroacetamides 10a–f and trimethyl phosphite using Michaelis–Arbuzov reaction.

**EXPERIMENTAL PART**

\(^1\)H, \(^{13}\)C, and \(^{31}\)P NMR spectra were obtained with a Bruker AC 250 spectrometer in CDCl\(_3\) as solvent. Chemical shifts are referred to TMS (\(^1\)H, \(^{13}\)C) as internal standard and to 85% H\(_3\)PO\(_4\) (\(^{31}\)P) as external standard. All coupling constants (\(J\)) are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), m (multiplet), and combination of these signals. IR spectra were recorded in potassium bromide pellets with a Perkin-Elmer FT-600 spectrometer. Melting points were measured in open capillary tubes on an Electro thermal apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 C, H, N analyzer and the determined values were within the acceptable limits of the calculated values. All reactions were monitored by TLC on silica Merck h60 F254 (Art. 5554) precoated aluminum plates and were developed by spraying with ninhydrin solution.

**Preparation of N-Acylsulfonamides 10a-f**

In a three-neck round bottomed flask equipped with a magnetic stirring bar and reflux condenser, sulfonamide (9a–f) (2 mmol) was dissolved in toluene (10 mL). Chloroacetyl chloride (0.41 g, 0.29 mL, 2 equiv., 4 mmol) and Lewis acid catalyst (0.4 g, 1.5 equiv., 3 mmol) were added dropwise with stirring. The reaction mixture was kept at a temperature of 50°C for 30 min and then heated to reflux for 3 h. After completing the reaction, the reaction mixture was cooled down to room temperature. The excess of chloroacetyl chloride was washed with water and the organic layer was separated. The solvent was removed under reduced pressure. The precipitated white product was filtered and recrystallized from diethyl ether.
N-(Phenyl)-Sulfamoyl-2-Chloroacetamide (10a)

White solid; yield: 60%; mp: 174–175°C. Rf = 0.7 (CH2Cl2/MeOH: 9/1). 1H NMR (CDCl3): δ = 8.05 (s, 1H, NH-CO), 7.63–7.25 (m, 5H, arom-H), 4.25 (s, 2H, CH2-Cl); 4.00 (s, 1H, NH-Ar). 13C NMR (CDCl3): δ = 160.1 (C=O), 136.6 (arom-C), 129.8 (arom-C), 125.9 (arom-C), 120.9 (arom-C), 41.4 (CH2- CO). IR (KBr): ν = 3350 (NH), 1725 (C=O), 1658 (C=C), 1365, 1159 cm⁻¹ (SO2). Anal. Calcd for C8H9N2O3SCl (248): C, 38.64; H, 3.65; N, 11.26. Found: C, 38.75; H, 3.95; N, 11.35%.

N-(3-Fluorophenyl)-Sulfamoyl-2-Chloroacetamide (10b)

White solid, yield: 55%, mp: 184–185°C. Rf = 0.75 (CH2Cl2/MeOH: 9/1). 1H NMR (CDCl3): δ = 8.20 (s, 1H, NH-CO), 6.91–7.23 (m, 4H, arom-H), 4.30 (s, 2H, CH2-Cl), 3.90 (s, 1H, NH-Ar). 13C NMR (CDCl3): δ = 166.7 (C=O), 163.0 (arom-C), 139.0 (arom-C), 129.6 (arom-C), 115.0 (arom-C), 110.5 (arom-C), 41.9 (CH2-CO). IR (KBr): ν = 3368 (NH), 1720.4 (C=O), 1658 (C=C), 1365, 1159 cm⁻¹ (SO2). Anal. Calcd for C8H8N2O3SClF (266): C, 36.03; H, 3.02; N, 13.29. Found: C, 36.19; H, 3.15; N, 13.05%.

N-(1-Phenylethyl)-Sulfamoyl-2-Chloroacetamide (10c)

White solid, yield: 65%, mp: 175–176°C, Rf = 0.7 (CH2Cl2/MeOH: 9/1). 1H NMR (CDCl3): δ = 8.69 (s, 1H, NH-CO), 7.50 (m, 5H, arom-H), 5.93 (d, J = 6.9 Hz, 1H, NH-CH), 4.67 (m, 1H, CH), 3.92 (m, 2H, CH2-Cl), 1.57 (d, J = 6.9 Hz, 3H, CH3). 13C NMR (CDCl3): δ = 165.5 (C=O), 145.7 (arom-C), 125.1 (arom-C), 126.9 (arom-C), 126.5 (arom-C), 45.3, C-H), 41.2 (CH2-CO), 19.0 (CH3). IR (KBr): ν = 3260 (NH), 1710 (C=O), 1642 (C=C), 1360, 1153 cm⁻¹ (SO2). Anal. Calcd for C10H13N2O3SCl (276): C, 43.40; H, 4.73; N, 10.12. Found: C, 43.52.; H, 4.89; N, 10.20%.

N-(4-Methoxyphenyl)-Sulfamoyl-2-Chloroacetamide (10d)

White solid, yield: 60%, mp: 175–176°C, Rf = 0.7 (CH2Cl2/MeOH: 9/1). 1H NMR (CDCl3): δ = 8.22 (s, 1H, NH-CO), 6.90–7.21 (m, 4H, arom-H), 4.28 (s, 2H, CH2-Cl), 4.00 (s, 1H, NH-Ar), 3.91 (s, 3H, OCH3). 13C NMR (CDCl3): δ = 135.9, 129.7, 125.3, 150.7, 162.5 (C=O), 150.1 (C-Ar), 130.2 (C-Ar), 125.3 (C-Ar), 115.3 (C-Ar), 55.0 (OCH3-Ar), 42.1 (CH2-CO). IR (KBr): δ = 3368 (NH), 1720.4 (C=O), 1658 (C=C), 1365, 1159 cm⁻¹ (SO2). Anal. Calcd for C9H10N2O4SCl (277): C, 38.78; H, 3.98; N, 10.05. Found: C, 38.65; H, 4.05; N, 10.15%.

N-(Cyclohexyl)-Sulfamoyl-2-Chloroacetamide (10e)

White solid, yield: 87%, mp: 178–179°C, Rf = 0.7 (CH2Cl2/MeOH: 9/1). 1H NMR (CDCl3): δ = 8.60 (s, 1H, NH-CO), 4.95 (d, J = 6.2 Hz, 1H, NH-cHex), 4.10 (s, 2H, CH2-Cl), 3.25 (m, 1H, CH-NH), 1.85 (m, 2H, CH2 of cHex), 1.55 (m, 2H, CH2 of cHex), 1.35 (m, 2H, CH2 of c-Hex), 1.27 (m, 4H, CH2 of c-Hex). 13C NMR (CDCl3): δ = 159.2 (C=O), 43.8 (CH of c-Hex), 42.9 (CH2-CO), 33.5 (CH2 of c-Hex), 25.9 (CH2 of c-Hex), 24.0 (CH2 of c-Hex). IR (KBr): ν = 3269 (NH), 1700 (C=O), 1368, 1150 cm⁻¹ (SO2).
Anal. Calcd for C₈H₁₅N₂O₃SCl (254): C, 37.72; H, 5.94; N, 11.00. Found: C, 37.65; H, 6.05; N, 11.15%.

N-(Benzy1)-Sulfamoyl-2-Chloroacetamide (10f)

White solid, yield: 60%, mp: 184–185°C, Rf = 0.65 (CH₂Cl₂/MeOH: 9/1). ¹H NMR (CDCl₃): δ = 8.10 (s, 1H, NH-CO), 7.65 (s, 1H, NH-Ar), 7.35–7.25 (m, 5H, arom-H), 4.25 (s, 2H, CH₂-Cl), 3.45 (d, J = 4.2 Hz, 2H, CH₂-Ar). ¹³C NMR (CDCl₃): δ = 160.8 (C=O), 141.6 (arom-C), 128.5 (arom-C), 126.9 (arom-C), 126.6 (arom-C), 43.7 (CH₂-NH), 41.4 (CH₂-CO). IR (KBr): ν = 3350 (NH), 1725 (C=O), 1658 (C=C), 1365, 1159 cm⁻¹ (SO₂). Anal. Calcd for C₉H₁₁N₂O₃SCl (262): C, 41.15; H, 4.22; N, 10.66. Found: C, 41.05; H, 4.35; N, 10.75%.

General Procedure for the Arbuzov Reaction

The trimethylphosphite (5 equiv., 4.96 mmol) and the corresponding compound 10a–f (1.1 equiv., 4.96 mmol) were heated at 110°C under argon and the resulting solution was heated to reflux for additional 5 h. The undesired products were removed by distillation. The residue was then purified by column chromatography on silica gel to give the corresponding compound 11a–f in good yield.

N-Phenyl-(1-(2-Dimethoxyphosphoryl)-Acetamide)-Sulfamide (11a)

Yellow oil, yield: 65%, Rf = 0.4 (CH₂Cl₂/MeOH: 9/1). ¹H NMR (CDCl₃): δ = 9.32 (s, 1H, NH-CO), 7.12–7.50 (m, 4H, arom-H), 6.90 (m, 1H, arom-H), 3.82 (s, 6H, OCH₃), 3.01 (d, J = 20.0 Hz, 2H, CH₂-PO). ¹³C NMR (CDCl₃): δ = 170.1 (C=O), 139.2 (arom-C), 129.6 (arom-C), 125.3 (arom-C), 120.9 (arom-C), 52.0 (OCH₃), 42.1 (CH₂-PO). ³¹P NMR (CDCl₃): δ = 27.3. IR (KBr): ν = 3350 (NH), 1725 (C=O), 1658 (C=C), 1365, 1159 cm⁻¹ (SO₂), 1251 cm⁻¹ (P=O). Anal. Calcd for C₁₀H₁₅N₂O₆SP (322): C, 37.26; H, 4.96; N, 8.69. Found: C, 37.35; H, 4.85; N, 8.75%.

N-3-Fluorophenyl-(1-(2-Dimethoxyphosphoryl)-Acetamide)-Sulfamide (11b)

Yellow oil, yield: 60%, Rf = 0.45 (CH₂Cl₂/MeOH: 9/1). ¹H NMR (CDCl₃): δ = 9.05 (s, 1H, NH-CO), 7.50 (m, 5H, arom-H), 5.55 (d, J = 6.2 Hz, 1H, NH-CH), 4.35 (m, 1H, CH), 3.80 (s, 6H, OCH₃), 2.92 (d, J = 19.1 Hz, 2H, CH₂-PO). ³¹P NMR (CDCl₃): δ = 28.3. IR (KBr): ν = 3368 (NH), 1720.4 (C=O), 1658 (C=C), 1365, 1159 (SO₂), 1245 cm⁻¹ (P=O). Anal. Calcd for C₁₀H₁₄N₂O₆SPF (340): C, 35.30; H, 4.15; N, 8.26. Found: C, 35.45; H, 4.05; N, 8.35%.

N-1-Phenylethyl-(1-(2-Dimethoxyphosphoryl)-Acetamide)-Sulfamide (11c)

Yellow oil, yield: 70%, Rf = 0.42 (CH₂Cl₂/MeOH: 9/1). ¹H NMR (CDCl₃): δ = 8.62 (s, 1H, NH-CO), 7.50 (m, 5H, arom-H), 5.55 (d, J = 6.2 Hz, 1H, NH-CH), 4.35 (m, 1H, CH), 3.80 (s, 6H, OCH₃), 2.92 (d, J = 19.1 Hz, 2H, CH₂-PO), 1.28 (d, J =
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6.9 Hz, 3H, CH$_3$). $^{13}$C NMR (CDCl$_3$): $\delta$ = 170.0 (C=O), 143.0 (arom-C), 128.1 (arom-C), 126.9 (arom-C), 126.5 (arom-C), 52.7 (OCH$_3$), 46.0 (CH), 42.2 (CH$_2$-PO), 19.0 (CH$_3$). $^{31}$P NMR (CDCl$_3$): $\delta$ = 27.9. IR (KBr): $\nu$ = 3260 (NH), 1710 (C=O), 1642 (C=C), 1360, 1153 (SO$_2$), 1250 cm$^{-1}$ (P=O). Anal. Calcd for C$_{12}$H$_{19}$N$_2$O$_6$SP (350): C, 41.14; H, 4.15; N, 8.00. Found: C, 41.25; H, 4.19; N, 8.05%.

N-4-Methoxyphenyl-(1-(2-Dimethoxyphosphoryl)-Acetamide)-Sulfamide (11d)

Yellow oil, yield: 75%, R$_f$ = 0.48 (CH$_2$Cl$_2$/MeOH: 9/1). $^1$H NMR (CDCl$_3$): $\delta$ = 8.82 (s, 1H, NH-CO), 6.90–7.35 (m, 4H, arom-H), 3.90 (s, 9H, OCH$_3$), 3.05 (d, $J$ = 20 Hz, 2H, CH$_2$-PO). $^{13}$C NMR (CDCl$_3$): $\delta$ = 170.5 (C=O), 153.0 (arom-C), 130.0 (arom-C), 125.0 (arom-C), 115.3 (arom-C), 56.0 (OCH$_3$-Ar), 52.3 (OCH$_3$), 42.8 (CH$_2$-PO). $^{31}$P NMR (CDCl$_3$): $\delta$ = 27.9. IR (KBr): $\nu$ = 3368 (NH), 1720 (C=O), 1658 (C=C), 1365, 1159 (SO$_2$), 1248 cm$^{-1}$ (P=O). Anal. Calcd for C$_{11}$H$_{17}$N$_2$O$_7$SP (352): C, 37.50; H, 4.86; N, 7.95. Found: C, 37.55; H, 4.98; N, 7.85%.

N-Cyclohexyl-(1-(2-Dimethoxyphosphoryl)-Acetamide)-Sulfamide (11e)

Yellow oil, yield: 70%, R$_f$ = 0.50 (CH$_2$Cl$_2$/MeOH: 9/1). $^1$H NMR (CDCl$_3$): $\delta$ = 8.65 (s, 1H, NH-CO), 3.91 (s, 6H, OCH$_3$), 3.66 (m, 1H, CH$_2$-NH), 2.80 (d, $J$ = 10.1, 2H, CH$_2$-PO), 1.85 (m, 2H, CH$_2$ of c-Hex), 1.55 (m, 2H, CH$_2$ of c-Hex), 1.35 (m, 2H, CH$_2$ of c-Hex), 1.28 (m, 4H, CH$_2$ of c-Hex). $^{13}$C NMR (CDCl$_3$): $\delta$ = 171.0 (C=O), 53.0 (OCH$_3$), 43.0 (CH of c-Hex), 42.1 (CH$_2$-PO), 32.0 (CH$_2$ of c-Hex), 25.0 (CH$_2$ of c-Hex), 24.0 (CH$_2$ of c-Hex). $^{31}$P NMR (CDCl$_3$): $\delta$ = 29.8. IR (KBr): $\nu$ = 3269 (NH), 1700 (C=O), 1368, 1150 (SO$_2$), 1245 cm$^{-1}$ (P=O). Anal. Calcd for C$_{10}$H$_{21}$N$_2$O$_6$SP (328): C, 36.58; H, 3.45; N, 8.53. Found: C, 36.65; H, 3.25; N, 8.85%.

N-Benzyl-(1-(2-Dimethoxyphosphoryl)-Acetamide)-Sulfamide (11f)

Yellow oil, yield: 65%, R$_f$ = 0.42 (CH$_2$Cl$_2$/MeOH: 9/1). $^1$H NMR (CDCl$_3$): $\delta$ = 8.82 (s, 1H, NH-CO), 7.25 (m, 5H, arom-H), 3.82 (s, 6H, OCH$_3$), 3.75 (d, $J$ = 4.2 Hz, 2H, CH$_2$-Ar), 3.09 (d, $J$ = 19.5 Hz, 2H, CH$_2$-PO). $^{13}$C NMR (CDCl$_3$): $\delta$ = 171.0 (C=O), 141.2 (arom-C), 128.6 (arom-C), 126.9 (arom-C), 126.6 (arom-C), 52.2 (OCH$_3$), 43.2 (CH$_2$-NH), 41.2 (CH$_2$-PO). $^{31}$P NMR (CDCl$_3$): $\delta$ = 27.9. IR (KBr): $\nu$ = 3350 (NH), 1725 (C=O), 1658 (C=C), 1365, 1159 (SO$_2$), 1249 cm$^{-1}$ (P=O). Anal. Calcd for C$_{11}$H$_{17}$N$_2$O$_6$SP (356): C, 41.25; H, 5.35; N, 8.75. Found: C, 41.35; H, 5.25; N, 8.85%.

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SUPPLEMENTAL MATERIAL

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