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AN EFFICIENT ONE-POT SYNTHESIS OF SOME NEW SUBSTITUTED 1, 2, 3, 5-THIATRIAZOLIDIN-4-ONE 1,1-DIOXIDES

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Abstract – A series of some new 1,2,3,5-thiatriazolidin-4-one 1,1-dioxides derivatives were synthesized by reacting respectively β-cyanohydrazines and phosphorylated hydrazine with chlorosulfonyl isocyanate in good yields. The structures of all the newly prepared compounds were confirmed by IR, ^{1}H, ^{13}C, ^{31}P-NMR spectral data and elemental analysis.

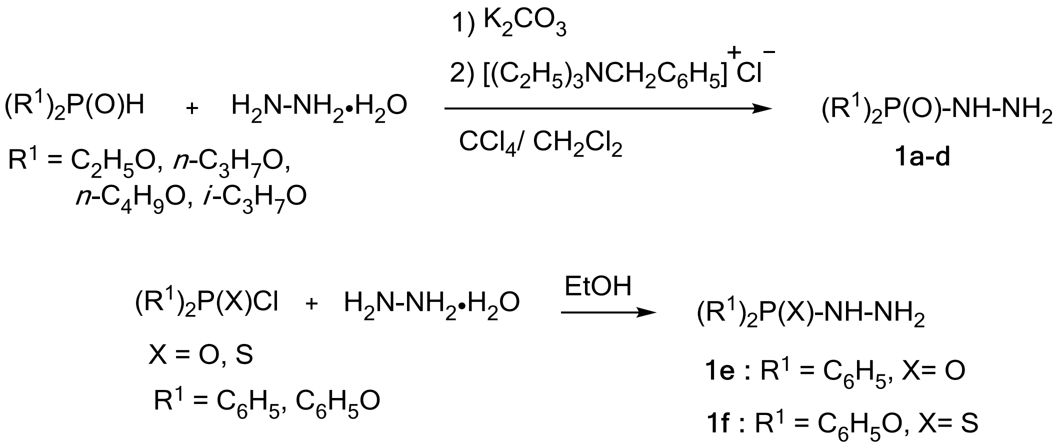
Sulfamide derivatives have boomed in recent years in the literature, following to their extensive use as pharmacophores and their interesting biological properties. Indeed, the sulfamide moiety, an important synthetic potential has emerged as a promising class of compounds in drug discovery.[1,2] Similarly, interest in the cyclic sulfamides, do not exist in nature, has allowed some researchers to develop new promising concepts and to discover and produce new active substances.[3,4] These compounds are well known in the medicinal chemistry field as a non-hydrolysable components peptidomimetics,[5,6] agonists of the 5–HT$_{ID}$ (rate controller serotonin)[7] and the HIV serineprotease.[8-11]

In the context of such collaboration and in continuation of our work on the synthesis of novel nitrogen and sulfur heterocyclic systems, we focused our studies on the preparation of series of five-membered heterocyclic compounds containing a sulfamide group. We describe for the first time the first example of a new class of heterocyclic 1,2,3,5-thiatriazolidin-4-one 1,1-dioxides. The new cyclic sulfamide is an interesting candidate for pharmaceutical purposes.

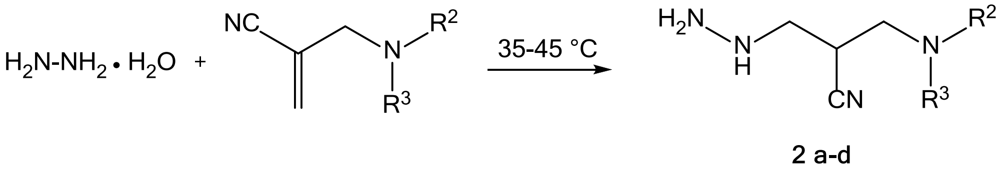
The heteroaromatic 1,2,3,5-thiatriazolidin-4-one 1,1-dioxides are a class of biologically active heterocyclic compounds.[12-14] However, only a few methods for synthesizing these compounds have been described.[15-17] One approach to the preparation of these heterocycles has been reported by S. D. Ziman by reacting thionyl chloride on semi or thiosemicarbazides.

Chlorosulfonyl isocyanate (**CSI**), discovered by Graf[18] is an heterocumulene of exceptional reactivity.[19] Until now, no reaction of this compound with phosphorylated hydrazine or β-cyanohydrazines has been reported.

Herein, we describe a facile one-pot synthesis of new substituted 1,2,3,5-thiatriazolidin-4-one 1,1-dioxides **3** and **4** in which phosphorylated hydrazine **1**, β-cyanohydrazines **2** and chlorosulfonyl isocyanate are employed as starting materials. These compounds which depicted in scheme 1 and scheme 2 were prepared according to the literature.[20-25]

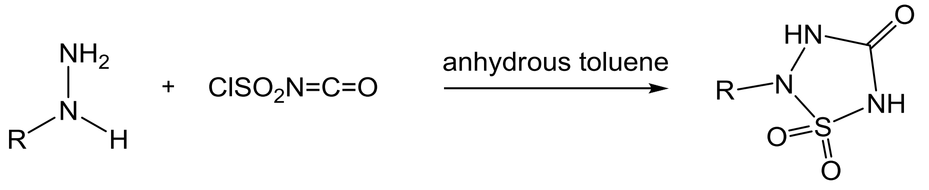


Scheme 1. The drawing represents the synthetic procedures of phosphorylated hydrazine



Scheme 2. Synthetic pathway for the preparation of β-cyanohydrazine

The desired compounds **3** and **4** were readily synthesized as shown in Scheme 3. Phosphorylated hydrazine **1** and β-cyanohydrazines **2** were prepared subsequently condensed with **CSI** in anhydrous toluene to affords 1,2,3,5-thiatriazolidin-4-one 1,1-dioxides **3** and **4**. In order to demonstrate the efficiency and generality of this protocol, we examined the reactions of various substituted hydrazine with **CSI** (Table 1). All substrates react to give the corresponding compounds **3** and **4** in good to excellent yields.



1: R = $(R^1)_2P(X)$ X = O, S

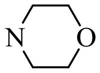
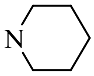
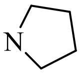
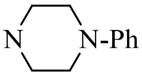
2: R = $-CH_2-CH(CN)-CH_2-N(R^2R^3)$

3: R = $(R^1)_2P(X)$, X = O, S

4: R = $-CH_2-CH(CN)-CH_2-N(R^2R^3)$

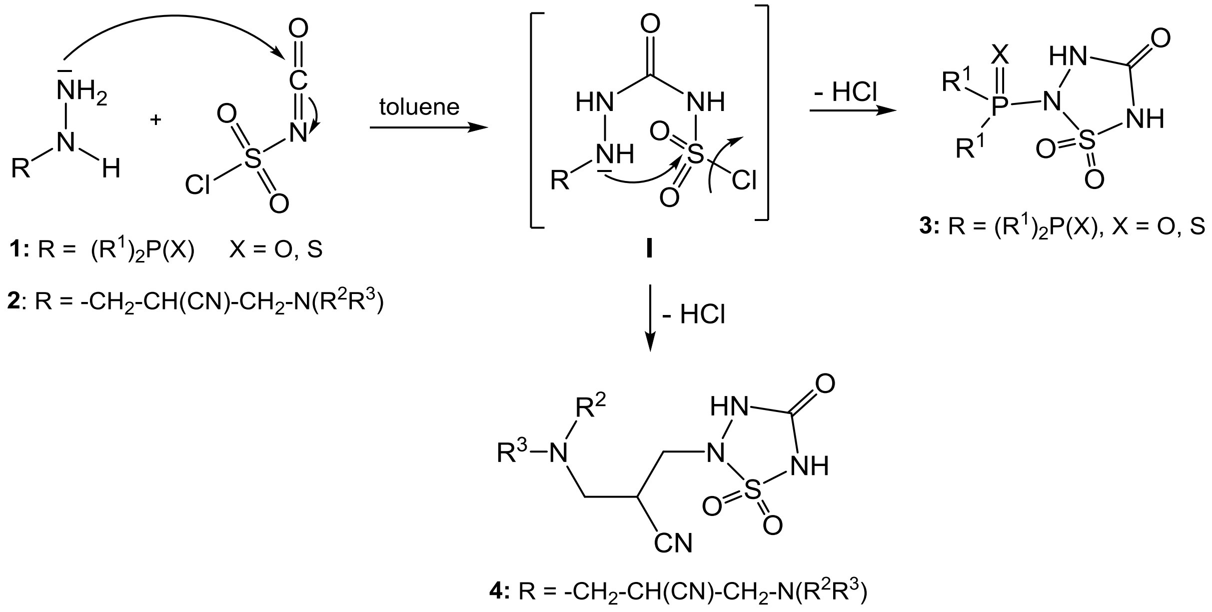
Scheme 3. Synthesis of 1,2,3,5-thiatriazolidin-4-one 1,1-dioxides **3** and **4**

Table 1. Substrate scope studies

Entry	R^1(**1a-f**),N-R^2R^3 (**2a-d**)	Product **3a-e** (X= O), **3f** (X= S)	Yield (%)[a]
1a	EtO	**3a**	79
1b	*n*-PrO	**3b**	71
1c	*n*-BuO	**3c**	77
1d	*i*-PrO	**3d**	69
1e	C_6H_5	**3e**	73
1f	C_6H_5O	**3f**	66
2a		**4a**	68
2b		**4b**	70
2c		**4c**	63
2d		**4d**	76

[a] Isolated yield.

A plausible mechanism for the formation of compounds **3** and **4** is depicted in (Scheme 4). The reaction was assumed to proceed by nucleophilic attack of the NH_2 group of hydrazine on the carbonyl group of **CSI**, giving intermediate **I** which then immediately yielded via an heterocyclization the correspondent 1,2,3,5-thiatriazolidin-4-one 1,1-dioxides.



1: R = $(R^1)_2P(X)$ X = O, S

2: R = $-CH_2-CH(CN)-CH_2-N(R^2R^3)$

3: R = $(R^1)_2P(X)$, X = O, S

4: R = $-CH_2-CH(CN)-CH_2-N(R^2R^3)$

Scheme 4. Reaction mechanism for the synthesis of compounds **3** and **4**

During this reaction the addition of chlorosulfonyl isocyanate was carried out at room temperature to avoid the attack of the free electron pair of the primary nitrogen on the sulfonic group, indeed after the addition of **CSI** the mixture was heated to facilitate the chloride departure. We found that these new heterocyclic compounds are relatively unstable to air and at room temperature. These compounds can be kept at cold under an argon atmosphere.

The structures of the compounds were established on the basis of their spectral data. The IR spectra show an absorption bands around 3419 and 3320 cm^{-1} which is assigned to the vibration of the NH group. There is another strong band at 1690 cm^{-1} which is attributed to the amide group. All ^{1}H- and ^{13}C-NMR data obtained for the compounds are presented in the experimental section. In ^{1}H-NMR spectra, we observed essentially the total disappearance of the signal of NH_2 group and the appearance of a new signal around 10 ppm characteristic of the protons of the amide group. ^{13}C-NMR chemical shifts of different types of atoms are consistent with the structure of the synthesized compounds. Analysis of the ^{13}C-NMR spectra shows the appearance of a new signal around 157 ppm attributed to the carbonyl of the amide group.

In summary, we have described in this paper the discovery of a simple and general route to synthesize some new 1,2,3,5-thiatriazolodin-4-one 1,1-dioxides scaffolds in moderate to excellent yields from corresponding substituted hydrazine and chlorosulfonyl isocyanate. Further studies on the bioactivity of the synthesized compounds are currently under way in our laboratory.

EXPERIMENTAL

Melting points were determined on a Buchi B-545 melting point apparatus and are uncorrected. All reactions were monitored by thin layer chromatography (TLC). IR spectra were recorded in the range 4000-600 cm^{-1} using KBr disks on a Perkin Elmer 1600 series FTIR spectrometer. ^{1}H, ^{31}P and ^{13}C-NMR spectra were recorded with DMSO-d_6 as the solvent, on a Bruker-300 spectrometer. The chemical shifts are reported in ppm relative to TMS (internal reference) for ^{1}H and ^{13}C-NMR and relative to 85% H_3PO_4 (external reference) for ^{31}P -NMR. Elemental analyses were carried out on EI Elemental Vario EL apparatus. The starting materials were prepared according to reported procedures.[20-25]

Typical experimental procedure for the synthesis of 1,2,3,5-thiatriazolodin-4-one 1,1-dioxides 3 and 4. To a well-stirred solution of substituted hydrazine (1 mmol) in dry toluene (10 mL) was added **CSI** (1 mmol) drop-wise over 2 min at room temperature and stirred for 30 min. The stirring of the reaction mixture was continued for 60 min at 60 °C. Resulting precipitate was filtered of in satisfactory purity.

3a: Hygroscopic white solid; mp 114-116 °C, Yield: 79%. IR (KBr, cm^{-1}): 3420, 3322 (-NH), 1685 (C=O), 1270 (P=O), 943 (S-N), 1345, 1138 (-NH-SO_2), ^{1}H-NMR (DMSO-d_6): 7.16 (br s, 1H) ; 9.86 (br s, 1H); 4.05 (m, 2H); 1.21 (m, 3H), ^{13}C-NMR (DMSO-d_6): 155.11, 65.24, 16.55, ^{31}P-NMR (DMSO-d_6): 1.10, Anal. Calcd for $C_5H_{12}N_3O_6PS$ (273.20): C, 21.98; H, 4.43; N, 15.38 ; P, 11.34 ; S, 11.74. Found: C, 21.93; H, 4.38; N, 15.42 ; P, 11.32.

3b: Hygroscopic white solid; mp 102-104 °C, Yield: 71%, IR (KBr, cm^{-1}): 3419, 3320 (-NH), 1690 (C=O), 1279 (P=O), 932 (S-N), 1340, 1132 (-NH-SO_2), ^{1}H-NMR (DMSO-d_6): 7.2 (br s, 1H); 9.94 (br s, 1H); 1.57 (m, 2H); 1.16 (m, 3H), 3.8 (m, 2H), ^{13}C-NMR (DMSO-d_6): 157.56, 64.52, 24.82, 16.77. ^{31}P-NMR (DMSO-d_6): 1.56, Anal. Calcd for $C_7H_{16}N_3O_6PS$ (301.25): C, 27.91; H, 5.35; N, 13.95; P, 10.28; S, 10.64. Found: C, 27.94; H, 5.29; N, 13.92; P, 10.25.

3c: Hygroscopic white solid; mp 87-89 °C, Yield: 77%, IR(KBr, cm^{-1}): 3423, 3318 (-NH), 1688 (C=O), 1281 (P=O), 940 (S-N), 1342, 1167 (-NH-SO2), ^{1}H-NMR (DMSO-d_6): 7.34 (br s, 1H); 9.98 (br s, 1H); 1.54 (m, 2H); 0.93 (m, 3H), 3.73 (m, 2H), 1.25 (m, 2H), ^{13}C-NMR (DMSO-d_6): 154.87, 68.87, 21.86, 16.58, 35.58. ^{31}P-NMR (DMSO-d_6): 1.73, Anal. Calcd for $C_9H_{20}N_3O_6PS$ (329.31): C, 32.83; H, 6.12; N, 12.76; P, 9.41; S, 9.74. Found: C, 32.85; H, 6.08; N, 12.77; P, 9.39.

3d: Hygroscopic white solid; mp 97-99 °C, Yield: 69%, IR (KBr, cm^{-1}): 3380, 3279 (-NH), 1686 (C=O), 1250 (P=O), 954 (S-N), 1338, 1165 (-NH-SO2), ^{1}H-NMR (DMSO-d_6): 7.18 (br s, 1H); 9.57 (br s, 1H); 3.9 (m, 1H); 1.4 (m, 6H). ^{13}C-NMR (DMSO-d_6): 157.96, 61.33, 19.76. ^{31}P-NMR (DMSO-d_6): 1.58, Anal. Calcd for $C_7H_{16}N_3O_6PS$ (301.25): C, 27.91; H, 5.35; N, 13.95; P, 10.28; S, 10.64. Found: C, 27.97; H, 5.33; N, 13.89; P, 10.32.

3e: Hygroscopic white solid; mp 139-141 °C, Yield: 73%, IR (KBr, cm^{-1}): 3417, 3281 (-NH), 1677 (C=O), 1257 (P=O), 958 (S-N), 1330, 1166 (-NH-SO2), ^{1}H-NMR (DMSO-d_6): 7.24 (br s, 1H); 9.54 (br s, 1H); 7.34-7.62 (m, 10H, Ar-H), ^{13}C-NMR (DMSO-d_6): 158.06, 129.02, 131.30, 132.39, 135.47. ^{31}P-NMR (DMSO-d_6): 25.33, Anal. Calcd for $C_{13}H_{12}N_3O_4PS$ (337.29): C, 46.29; H, 3.59; N, 12.46; P, 9.18; S, 9.51. Found: C, 46.33; H, 3.53; N, 12.44; P, 9.21.

3f: Hygroscopic white solid; mp 156-158 °C, Yield: 66%, IR (KBr, cm^{-1}): 3385, 3270 (-NH), 1680 (C=O), 1279 (P=S), 963 (S-N), 1352, 1143 (-NH-SO_2), ^{1}H-NMR (DMSO-d_6): 6.98 (br s, 1H); 9,88 (br s, 1H); 7,14-7,42 (m, 10H, Ar-H), ^{13}C-NMR (DMSO-d_6): 154,66, 149,85, 130,03, 126,56, 120,54. ^{31}P-NMR (DMSO-d_6): 62.61. Anal. Calcd for $C_{13}H_{12}N_3O_5PS_2$ (385.35): C, 40.42; H, 3.14; N, 10.90; P, 8.04; S, 16.64. Found: C, 40.41; H, 3.16; N, 10.98; P, 8.12.

4a: Hygroscopic yellow solid; mp 121-123 °C, Yield: 68%, IR (KBr, cm^{-1}): 3329, 3267 (-NH), 1691 (C=O), 962 (S-N), 1340, 1164 (-NH-SO_2), 2173 (CN), ^{1}H-NMR (DMSO-d_6): 7.29 (br s, 1H); 9.77 (br s, 1H), 3.77(m, 2H), 3.65 (m, 1H), 2.66 (m, 2H), 3.54 (m, 4H), 2.25 (m, 4H), ^{13}C-NMR (DMSO-d_6): 155.81, 47.62, 118,36, 30.57, 55.64, 52.91, 72.58. Anal. Calcd for $C_9H_{15}N_5O_4S$ (289.31): C, 37.36; H, 5.23; N, 24.21; S, 11.08. Found: C, 37.29; H, 5.31; N, 24.19.

4b: Hygroscopic yellow solid; mp 113-115 °C, Yield: 70%, IR (KBr, cm^{-1}): 3415,3327 (-NH), 1684 (C=O), 965 (S-N), 1355, 1157 (-NH-SO_2), 2170 (CN), ^{1}H-NMR (DMSO-d_6): 7.32 (br s, 1H); 9.81 (br s, 1H), 3.74 (m, 2H), 3.61 (m, 1H), 2.65 (m, 2H), 1.38 (m, 6H), 2.34 (m, 4H), ^{13}C-NMR (DMSO-d_6): 157.52, 47.38, 118,25, 33.72, 56.85, 54.28, 26.61, 29.34. Anal. Calcd for $C_{10}H_{17}N_5O_3S$ (287,13): C, 41.80; H, 5.96; N, 24.37; S, 11.16. Found: C, 41.76; H, 5.98; N, 24.35.

4c: Hygroscopic yellow solid; mp 107-109 °C, Yield: 63%, IR (KBr, cm^{-1}): 3432, 3312 (-NH), 1693 (C=O), 953 (S-N), 1360, 1162 (-NH-SO_2), 2175 (CN), ^{1}H-NMR (DMSO-d_6): 7.36 (br s, 1H); 9.87 (br s, 1H), 3.75 (m, 2H), 3.63 (m, 1H), 2.81 (m, 2H), 1.89 (m, 4H), 2.77 (m, 4H), ^{13}C-NMR (DMSO-d_6): 156.92, 49.32, 118,55, 32.11, 57,44, 54.32, 26.78. Anal. Calcd for $C_9H_{15}N_5O_3S$ (273.31): C, 39.55; H, 5.53; N, 25.62 ; S, 11.73. Found: C, 39.51; H, 5.55; N, 25.67.

4d: Hygroscopic yellow solid; mp 128-130 °C, Yield: 76%, IR (KBr, cm^{-1}): 3419, 3275 (-NH), 1698 (C=O), 959 (S-N), 1357, 1132 (-NH-SO_2), 2173 (CN), ^{1}H-NMR (DMSO-d_6): 7.16 (br s, 1H); 9.94 (br s, 1H), 3.92(m, 2H), 3.58 (m, 1H), 2.63 (m, 2H), 2.44 (m, 4H), 2.75 (m, 4H), 7.18 (m, 5H),^{13}C-NMR (DMSO-d_6): 155.72, 48.31, 118,61, 43.22, 55,16, 51.62, 53.11, 128.82, 129.52, 132.08, 134.13. Anal. Calcd for $C_{15}H_{20}N_6O_3S$ (364.42): C, 49.44; H, 5.53; N, 23.06; S, 8.80. Found: C, 49.45; H, 5.51; N, 23.13.

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