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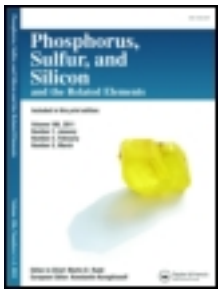

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Synthetic modification of 1,3-thiazolidin-4-one 1,1-dioxides

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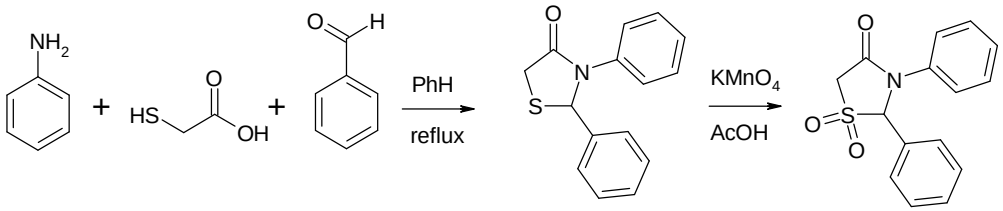

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Abstract

The reactivity of EWG (electron withdrawing group)-activated methylene group in 1,3-thiazolidin-4-one 1,1-dioxides were investigated. Novel derivatives of 1,3-thiazolidin-4-one 1,1-dioxides were prepared (the heterocyclic core was modified with carboxamide and carboxthioamide moieties as carbonyl group analogues). The products, which have functional groups for possible future modifications, are described and characterized.

Introduction

The structural and therapeutic diversity, coupled with commercial viability, of small heterocyclic molecules has fascinated organic and medicinal chemists for a long period of time. Amongst the heterocyclic systems, 1,3-thiazolidin-4-one 1,1-dioxides are a biologically

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important scaffold which is known to be important for display of several biological activities. Some of the prominent biological responses attributed to this skeleton are cytotoxicity [1] (**1**), CNS-mediators inhibition [2] (**2**) and antiproliferation [3] (**3**).

This diversity in the biological response profiles of 1,3-thiazolidin-4-one 1,1-dioxides attracts the attention of many researchers to explore the possibility of the use this scaffold in the design of multifunctional drug-like molecules [4, 5, 6, 7, 8, 9].

The desired compounds are being synthesized by a cyclization reaction [10, 11]. This method is limited by the availability of the corresponding mercaptoacetic acid and the stability of functional groups in carbonyl - and amino components under the reaction conditions. That is why not only the synthesis, but also the post-synthetic modification of a heterocyclic system is very important. So far, insufficient attention has been paid to the synthetic modification of the 1,3-thiazolidin-4-one 1,1-dioxides [9, 12, 13, 14]. However, the structure of these scaffolds enables us to introduce different substituents in the fifth position, such as carbonyl group equivalents including the carboxamide group. Moreover, this makes it possible to prepare the molecules with pre-determined biological properties.

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Results and discussion

2,3-diphenyl-1,3-thiazolidin-4-one (**4**) 1,1-dioxide was chosen as a model compound. Compound **4** was obtained by three-component reaction of aniline, mercaptoacetic acid and benzaldehyde followed by subsequent oxidation of 2,3-diphenyl-1,3-thiazolidin-4-one [12, 15] (Scheme 1).

It is well-known that the carbonyl group, or its equivalents, are amongst the most frequently used functional groups in synthetic organic chemistry and that is the reason we decided to obtain some carbonyl derivatives. DMF-DMA (*N*,*N*-dimethylformamide dimethyl acetal), $POCl_3$/DMF, triethylformate, phenyl isocyanate and phenyl isothiocyanate and benzoic acid in the presence of a coupling additive (Scheme 2) were chosen for modification.

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The starting compound **4** easily forms enamino-derivative (**5**) in DMF at room temperature (Scheme 3).

Under Vilsmeier-Haack reaction conditions we didn't obtain compound **5*** instead the main product was identified as **5**.

The product **6** was obtained by the treatment of model compound with triethyl orthoformate in acetic anhydride as a solvent over 5 h (Scheme 4).

In the ^{1}H NMR spectra of derivatives **5** and **6** we could see the anticipated difference in chemical shifts for proton at the double bond (0.5 ppm), that may be explained by differences in the electronegativities of nitrogen and oxygen.

The carboxylic group is a starting motif for the synthesis of a variety of other derivatives such as esters, amides, hydrazones. 1,3-Thiazolidin-4-one 1,1-dioxide also readily reacts with electrophiles such as phenyl isothiocyanate and phenyl isocyanate. As a result, the corresponding amide **7** and thioamide **8** were obtained (Scheme 5).

It should be noted, that compound **4** can be acylated by arylcarboxylic acids in the presence of coupling agents (Scheme 6). The best result was obtained with the EDC/DMAP system (Table 1).

Experimental

General data. Solvents were purified according to standard methods [16]. All commercially available chemicals were purchased from Aldrich and Merck. The ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100MHz) spectra were recorded on a Varian Gemini spectrometer, using DMSO-d6. All chemical shifts are reported in ppm relative to TMS. IR spectra were recorded on spectrometer Nicolet Nexus 470 in tablets KBr. Mass spectra were recorded on a VG micro mass 7070H spectrometer in chemical ionization mode (APCI). Melting points were determined through a Fisher–Johns apparatus and are uncorrected. Elemental analyses (C, H, N) determined by means of a Perkin–Elmer 240 CHN elemental analyzer.

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5-[(Dimethylamino)methylidene]-2,3-diphenyl-1,3-thiazolidin-4-one 1,1 – dioxide (5)

To a 1,3-thiazolidin-4-one 1,1-dioxide (1 mmol) in dry DMF (1 mL) DMF-DMA (1.3 mmol) was added, and the mixture was stirred at room temperature overnight. The precipitate was filtered off and washed with hexane. The product was obtained as white powder.

Yield 80%. M.p. 224-226ºC. ^{1}H NMR (ppm): 3.23 (s, 3H), 3.30 (s, 3H), 6.51 (s, 1H), 7.05-7.45 (m, 10H), 7.73(s, 1H). ^{13}C NMR (ppm): 41.5, 47.1, 78.7, 92.5, 124.1, 124.2, 128.2, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 129.3, 131.1, 137.3, 152.4, 162.7. MS: m/z 343.2 (M+1). Anal. calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.14%; H, 5.3%; N, 8.18%. Found: C, 63.11%; H, 5.28%; N, 8.19%

5 -(Ethoxymethylidene) - 2, 3 - diphenyl -1,3-thiazolidin-4-one 1,1 – dioxide (6)

The mixture of 1,3-thiazolidin-4-one 1,1-dioxide (1 mmol), triethyl orthoformate (5 mmol) and acetic anhydride (5 mmol) was refluxed for 5 h, after this the mixture was cooled down. The precipitate was filtered off and washed with hexane. The product was obtained as white powder.

Yield 75%. M.p. >250ºC. ^{1}H NMR (ppm): 1.32 (t, J = 7.2 Hz, 3H), 4.59 (q, J = 6.8 Hz, 2H), 6.69 (s, 1H), 7.15-7.43 (m, 10H), 8.23 (s, 1H). ^{13}C NMR (ppm): 15.2, 74.2, 79.6, 106.3, 125.0, 126.3, 128.6, 128.6, 128.7, 128.7, 128.7, 128.7, 128.8, 129.6, 129.7, 136.2, 160.1, 165.1. MS: m/z 344.1 (M+1). Anal. calcd. for $C_{18}H_{17}NO_4S$: C, 62.96%; H, 4.99%; N, 4.08%. Found: C, 62.98%; H, 4.97%; N, 4.1%.

4-Oxo-N,2,3-triphenyl-1,3-thiazolidine-5-carboxamide 1,1-dioxide (7)

To a solution of DBU (1 mmol) in dry DMF (1 mL) solution of the 1,3-thiazolidin-4-one 1,1-dioxide (1 mmol) and phenyl isocyanate (1 mmol) in dry DMF (1.5 mL) were added. The mixture was stirred overnight and then 20 mL 5% HCl were added, the precipitate was filtered off, washed with water and dried. The product was obtained as white powder.

Yield 80%. M.p. 203-205ºC. ^{1}H NMR (ppm): 7.26-7.47 (m, 15H), 7.82-7.84 (m, 2H), 12.51 (s, 1H). ^{13}C NMR (ppm): 72.6, 79.2, 122.1, 122.2, 122.6, 122.7, 124.5, 124.9, 125.2, 127.3, 127.3, 127.6, 128.5, 128.6, 130.3, 130.3, 131.8, 131.9, 139.7, 143.3, 161.5, 162.6. MS: m/z 407.1 (M+1). Anal. calcd. for $C_{22}H_{18}N_2O_4S$: C, 65.01%; H, 4.46%; N, 6.89%. Found: C, 65.03%; H, 4.47%; N, 6.87%.

4-Oxo-N,2,3-triphenyl-1,3-thiazolidine-5-carbothioamide 1,1-dioxide (8)

To a solution of DBU (1 mmol) in dry DMF (1 mL) solution of the 1,3-thiazolidin-4-one 1,1-dioxide (1 mmol) and phenyl isothiocyanate (1 mmol) in dry DMF (1.5 mL) were added. The

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mixture was stirred overnight and then 20 mL 5% HCl were added, the precipitate was filtered off, washed with water and dried. The product was obtained as white powder.

Yield 85%. M.p.168-170ºC. ^{1}H NMR (ppm): 7.22-7.44 (m, 15H), 7.81-7.83 (m, 2H), 12.71 (s, 1H). ^{13}C NMR (ppm): 71.9, 83.6, 122.9, 123.0, 124.9, 125.1, 125.1, 125.9, 126.8, 126.9, 127.4, 127.5, 128.8, 128.9, 130.6, 130.7, 132.2, 132.2, 139.3, 144.1, 160.9, 168.59. MS: m/z 423.3 (M+1). Anal. calcd. for $C_{22}H_{18}N_2O_3S_2$: C, 62.54%; H, 4.29%; N, 6.63%. Found: C, 62.56%; H, 4.30%; N, 6.65%.

5-(2-Chloro-4-fluorobenzoyl)-2,3-diphenyl-1,3-thiazolidin-4-one 1,1-dioxide (9)

The mixture of 1,3-thiazolidin-4-one 1,1-dioxide (1 mmol), 2-chloro-4-fluorobenzoic acid (1 mmol), EDC (1 mmol), DMAP (1 mmol), DMF (3 mL) was stirred at room temperature for 120 h, then water was added and the precipitate was filtered off, washed with 5% HCl and dried. The product was obtained as white powder.

Yield 70%.M.p.158-160ºC. ^{1}H NMR (ppm): 6.45 (s, 1H), 7.03-7.56 (m, 14H).^{13}C NMR (ppm): 79.1, 113.9, 114.2, 123.0, 124.4, 124.5, 124.7, 126.7, 127.5, 128.1, 128.4, 128.5, 128.5, 128.6, 128.6, 129.1, 129.4, 129.7, 130.1, 163.9, 173.3, 193.0. MS: m/z 444.0 (M+1). Anal. calcd. for $C_{22}H_{15}ClFNO_4S$: C, 59.53%; H, 3.41%; N, 3.16%. Found: C, 59.55%; H, 3.43%; N, 3.14%.

Conclusions

The possible ways of synthetic modification of 1,3-thiazolidin-4-one 1,1-dioxides were described. DMF-DMA, $POCl_3$/DMF, triethyl orthoformate, phenyl isocyanate and phenyl isothiocyanate, benzoic acid in the presence of coupling reagents were used as electrophilic reagents.

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Acknowledgments

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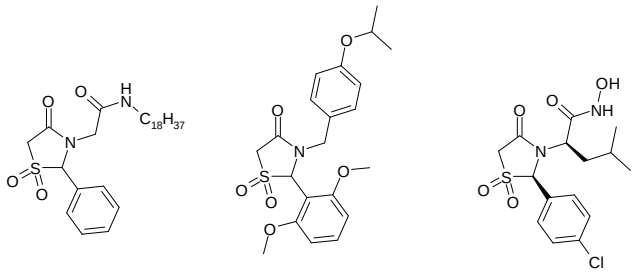
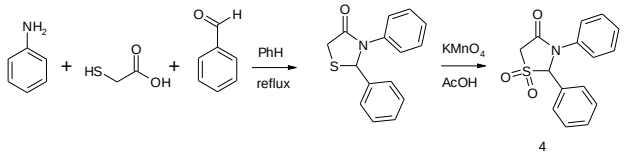
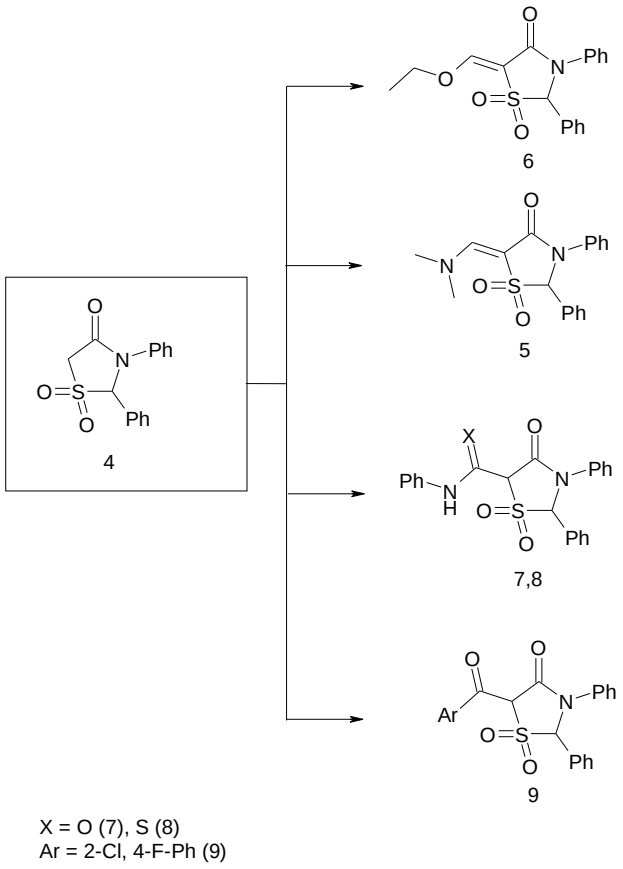
Figure 1. Some 1,3-thiazolidin-4-one 1,1-dioxides which demonstrate high biological activity



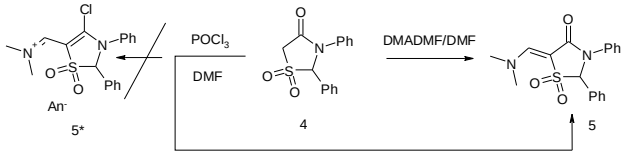
Scheme 1. Synthesis of a model compound



Scheme 2. Possible ways of modification



Scheme 3. Synthesis of enamino derivative of **5**



Scheme 4. Synthesis of **6**

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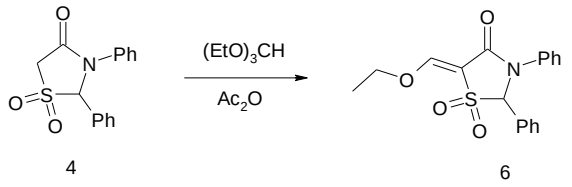
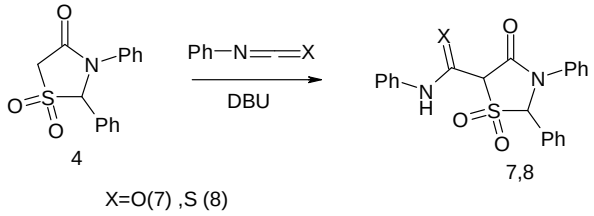


Scheme 5. Synthesis corresponding amide and thioamide



Scheme 6. The acetylation of **4**

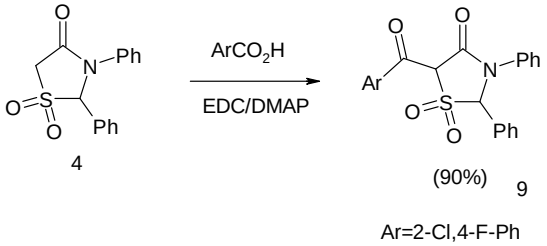


Table 1.

Reagent (solvent DMF)	Time, h	Yield of product, %
CDI	120	Not detected
EDC	120	30
EDC/DMAP	120	90

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