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Short Note

2-Benzoyl-4-phenyl-1,2,5-thiadiazol-3(2*H*)-one 1,1-Dioxide

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Abstract: 3,5-Diphenyl-4*H*-1,2,6-thiadiazin-4-one treated with *meta*-chloroperoxybenzoic acid undergoes an oxidative ring contraction to give 2-benzoyl-4-phenyl-1,2,5-thiadiazol-3(2*H*)-one 1,1-dioxide in a 29% yield, the structure of which is supported by single-crystal X-ray diffraction analysis and the available spectroscopic data.

Keywords: heterocycle; thiadiazine; thiadiazole; ring contraction; sulfone; oxidation

1. Introduction

1,2,5-Thiadiazoles are well-studied heterocycles with numerous applications in medicinal chemistry and materials science. Their chemistry and applications have been reviewed [1,2]. Examples of 1,2,5-thiadiazole-containing drugs are the antihypertensive drug Timolol and Tizanidine used in the treatment of multiple sclerosis (Figure 1). S-Oxidized 1,2,5-thiadiazole 1,1-dioxides also have many applications and selected examples act as pan-Kras inhibitors [3], indoleamine 2,3-dioxygenase inhibitors [4] and histamine H2-receptor antagonists (*cf.* compound **1**, Figure 1) [5].

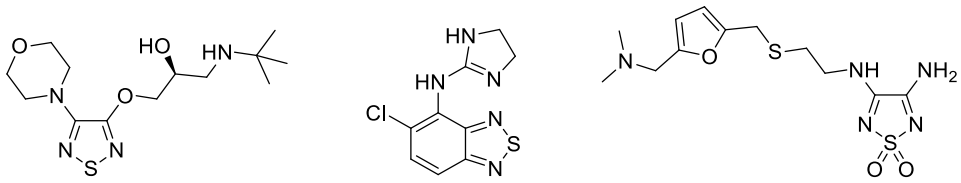

Figure 1. 1,2,5-Thiadiazole-containing drugs and an example of a 1,2,5-thiadiazole 1,1-dioxide with biological activity.

During our studies on 4*H*-1,2,6-thiadiazines [6], we discovered several unexpected ring contractions to give 1,2,5-thiadiazoles (Scheme 1): The first discovery involved the acid and/or thermal mediated double Wagner−Meerwein-mediated ring contraction of 3′5′-diarylspiro(benzo[*d*][1,3]dioxole-2,4′-[1,2,6]thiadiazines) **2** to give 3-aryl-4-(2-arylbenzo[*d*][1,3]dioxol-2-yl)-1,2,5-thiadiazoles **3** in near-quantitative yields [7]. Subsequently, we discovered that heating a solution of benzo[*e*][1,2,6]thiadiazino[3,4-*b*][1,4]diazepin-10(11*H*)-one (**4**) led to the formation of 2-(4-chloro-1,2,5-thiadiazol-3-yl)-quinazolin-4(3*H*)-one (**5**) [8]. More recently, we reported the photochemically mediated oxidative ring contraction of 1,2,6-thiadiazines **6** to 1,2,5-thiadiazol-3(2*H*)-one 1-oxides **7** under ambient conditions [9]. The reaction mechanism was revealed as a chemoselective [3 + 2] cycloaddition forming an endoperoxide, followed by ring contraction with selective carbon atom excision and complete atom economy.

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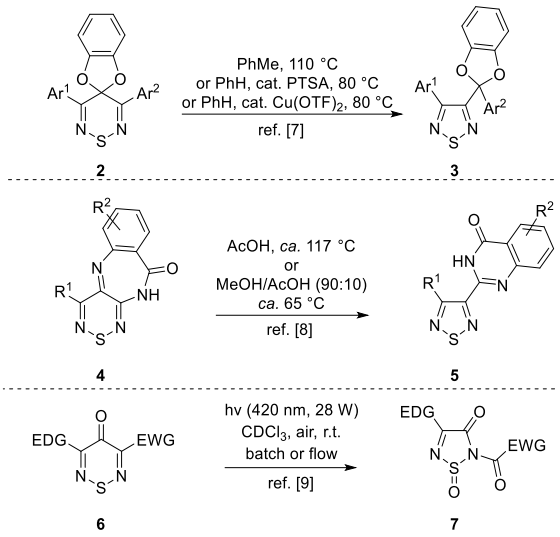
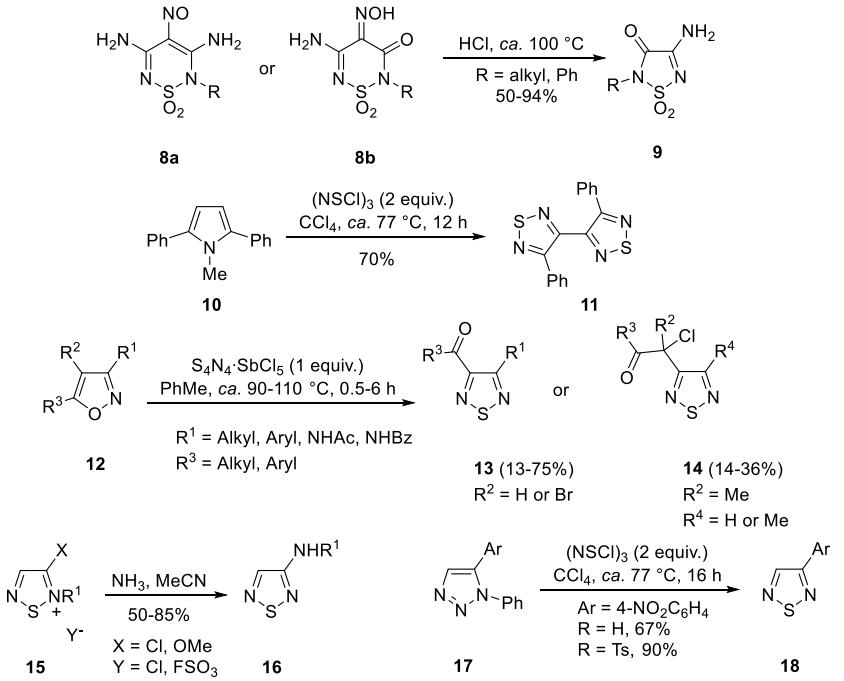


Scheme 1. Ring contractions of 4*H*-1,2,6-thiadiazines to various 1,2,5-thiadiazole scaffolds [7–9].

Aside from our work, only one synthesis of 1,2,5-thiadiazoles by ring transformations of six-membered rings is known: the ring contraction of 1,2,6-thiadiazine 1,1-dioxides **8** with strong acid to give thiadiazolinones **9** in a low yield [10] (Scheme 2). In contrast, there are several methods that start from five-membered rings. *N*-Alkylpyrrole **10** can under a cycloaddition reaction with trithiazyl trichloride to afford 1,2,5-bithiadiazole **11** [11] (Scheme 2). Substituted isoxazoles **12** can react with a tetrasulfur tetranitride–antimony pentachloride complex to afford 3-substituted 1,2,5-thiadiazoles **13** and **14** in medium yields [12] (Scheme 2). Thiadiazoliums **15** can be converted to thiadiazoles **16** by treatment with ammonia [13] (Scheme 2). Some electron-poor 1,2,3-triazoles **17** were converted to 1,2,5-thiadiazoles **18** by reaction with trithiazyl trichloride [14] (Scheme 2).



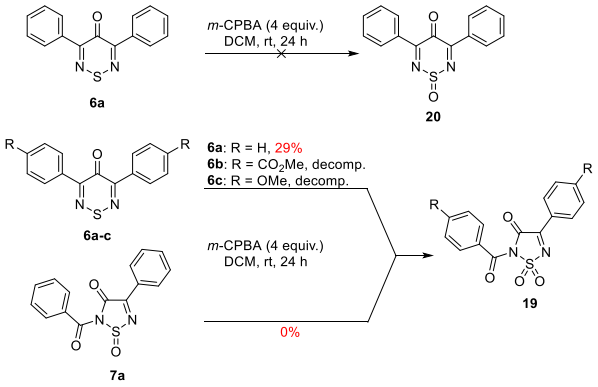
Scheme 2. Syntheses of 1,2,5-thiadiazoles by ring transformations.

Herein, we report the ring contraction of 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-one (**6a**) to 2-benzoyl-4-phenyl-1,2,5-thiadiazol-3(2*H*)-one 1,1-dioxide (**19**), mediated by the treatment of the former with *meta*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane (DCM).

This transformation furthers our understanding of the reactivity of thiadiazines and aligns with the broader theme of exploring novel and unexpected pathways in sulfur–nitrogen heterocycle chemistry.

2. Results and Discussion

Recently, we studied S-oxidations of 1,2,6-thiadiazines to access sulfoxide and sulfone analogs [15,16]. In an attempt to explore the reactivity of thiadiazine **6a** towards alternative oxidants, we expected to obtain thiadiazine sulfoxide **20** (Scheme 3). However, an unexpected discovery was made: when *m*-CPBA (four equiv. in total) was added to a DCM solution (C = 37.5 mM) of thiadiazine **6a**, a gradual color change (from yellow to colorless) was observed over 24 h. This was not consistent with the structure of sulfoxide **20**, as typically thiadiazine sulfoxides are colored [15,16]. Upon working up the reaction mixture, colorless needles [mp 172–173 °C (from Et_2O)] were isolated in a 29% yield. HRMS [*m*/*z* 315 (MH^+)] revealed the addition of "O_2", suggesting oxidation had occurred, while the compound's lack of color [λ_{max}(DCM) 295 nm, log ε 3.72] indicated a loss of the thiadiazine chromophore. The IR spectrum revealed two C=O stretching bands at 1772 and 1681 cm^{-1} and a strong band at 1300 cm^{-1}, suggesting the presence of a sulfone functionality. ^1H and ^{13}C NMR spectroscopy (see Supplementary Materials) supported an asymmetric structure and were similar to the spectra of 2-benzoyl-4-phenyl-1,2,5-thiadiazol-3(2*H*)-one 1-oxide (**7a**) [8]. Furthermore, similar to thiadiazolone **7a**, the product decomposed on silica.



Scheme 3. Reactions of thiadiazines **6a–c** and thiadiazole 1-oxide **7a** with *m*-CPBA.

X-Ray quality single crystals were prepared via the slow evaporation of an ethereal solution (5 mg in 1 mL) at ca. 20 °C, in the dark under air, and the structure was fully elucidated by single-crystal X-ray diffraction studies, revealing it to be the ring contracted sulfone, 2-benzoyl-4-phenyl-1,2,5-thiadiazol-3(2*H*)-one 1,1-dioxide (**19**) (Figure 2).

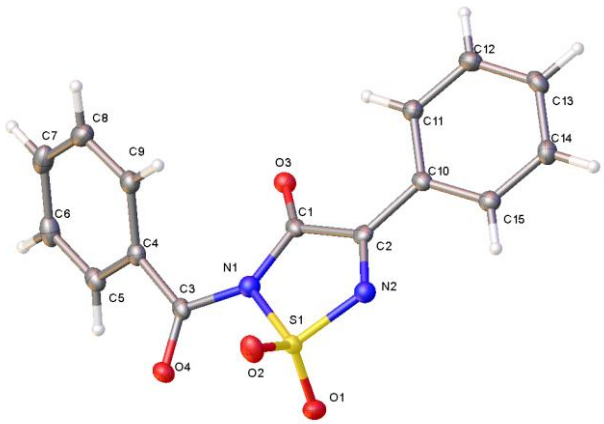


Figure 2. Single-crystal structure of 2-benzoyl-4-phenyl-1,2,5-thiadiazol-3(2*H*)-one 1,1-dioxide (**19**) [CCDC: 2168265].

The thiadiazole moiety is nearly planar with the plane defined by C1 N1 S1 N2 C2 with an RMSD of 0.033 Å. This plane is inclined at 15.954(8)° to the C bound Ph. However, the plane of the phenyl substituent of the benzoyl group is substantially out of the thiadiazole plane at 49.74(4)°. The carbonyl (C3 O4 N1 C4) is closer to coplanar with the normal thiadiazole plane to normal plane angle, 16.485(9)°, and twisted with respect to the 4-phenyl substituent at 37.12(3)°. The carbonyl oxygen of the thiadiazole moiety makes an intramolecular CH···O hydrogen bond with the phenyl H where C11···O3 is 2.943 Å. There are no significant intermolecular contacts.

Interestingly, treating pure sulfoxide **7a** with *m*-CPBA in DCM under similar reaction conditions led to no reaction and quantitative recovery of the starting material (Scheme 3). Tentatively, this suggested that the reaction mechanism for the formation of sulfone **19** did not involve the formation of sulfoxide **6a**, and that the transformation follows a different pathway. Moreover, treatment of either *para*-substituted substrates dimethyl 4,4′-(4-oxo-4*H*-1,2,6-thiadiazine-3,5-diyl)dibenzoate (**6b**) or 3,5-bis(4-methoxyphenyl)-4*H*-1,2,6-thiadiazin-4-one (**6c**) to the same reaction conditions gave complex reaction mixtures (by ^{1}H NMR spectroscopy), and no products could be isolated (Scheme 3). Studies are currently underway to further investigate this ring contraction.

3. Materials and Methods

All chemicals were commercially available except those whose synthesis is herein described. Anhydrous $MgSO_4$ was used for drying organic extracts and all volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial glass-backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of flash chromatography was used throughout for all non-TLC scale chromatographic separations using Merck Silica Gel 60 (less than 0.063 mm). Melting points were determined using a Stuart SMP10 digital melting point apparatus. Small-scale (μL) liquid handling measurements were made using variable-volume (1.00–5000.00 μL) single channel Gilson PIPETMAN precision micropipettes (Gilson, Middleton, WI, USA). The solvents used for recrystallisation are indicated after the melting point. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FTIR spectrometer (Thermo Scientific, Waltham, MA, USA) with an iD5 ATR accessory and broad, strong, medium and weak peaks are represented by b, s, m and w, respectively. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III HD machine [at 400 and 100 MHz, respectively (Bruker, Billerica, MA, USA)]. An AVANCE III 300 MHz NMR Spectrometer was also used for reaction monitoring. Chemical shifts (δ) are expressed in ppm. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br s = broad singlet). Deuterated solvents were used for homonuclear locks and the signals are referenced to the deuterated solvent peaks. For the acquisition of mass spectra, the samples were prepared as detailed below and analyzed by positive ion nanoelectrospray (nES) using a Thermo Scientific™ LTQ Orbitrap XL™ ETD Hybrid Ion Trap-Orbitrap Mass Spectrometer (Thermo Scientific, Waltham, MA, USA). For the X-ray crystallography, each crystal was coated in paraffin oil, mounted on a Molecular Dimensions Litholoop and placed directly into the cold stream of a Bruker D8 Venture diffractometer (Bruker, Billerica, MA, USA). Single-crystal X-ray diffraction data were collected using either a Cu-Kα (λ = 1.5418 Å) IμS 3.0 microfocus source or a Mo sealed tube with Triumph monochromator, using Bruker's APEX3 program suite [17], with the crystal kept at 100.0 K during data collection. The structures were solved using Olex2 [18], using the SHELXT structure solution program [19], using Intrinsic Phasing, and refined with the SHELXL refinement package using Least Squares minimization [20]. The starting materials 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-one **6a**, dimethyl 4,4′-(4-oxo-4*H*-1,2,6-thiadiazine-3,5-diyl)dibenzoate (**6b**) and 3,5-bis(4-methoxyphenyl)-4*H*-1,2,6-thiadiazin-4-one (**6c**) were made according to the literature procedure [21].

*2-Benzoyl-4-phenyl-1,2,5-thiadiazol-3(2H)-one 1,1-dioxide (***19***)*

To a stirred solution of 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-one (**6a**) (20.0 mg, 0.075 mmol) in DCM (5 mL) at ca. 20 °C was added one portion of *m*-CPBA (2 equiv.). After 30 min, the mixture still contained starting material (by ^{1}H NMR); however, the introduction of a further portion of *m*-CPBA (2 equiv.) led to the complete consumption of the starting material within 30 min. After the reaction was complete, the mixture was transferred to a separation funnel, the organic layer was separated and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resulting residue was washed with cold Et_2O (3 × 1 mL) and volatiles were removed under reduced pressure to afford the *title compound* **19** (6.8 mg, 29%) as colorless needles, mp (hot-stage) 172–173 °C (Et_2O); λ_{max}(DCM)/nm 295 (log ε 3.72); ν_{max}/cm^{-1} 1772m (C=O), 1681s (C=O), 1597w, 1507w, 1576w, 1560s, 1491w, 1449m, 1416m, 1389s, 1300m, 1258s, 1207s, 1193s, 1177s, 1067m, 1021m, 923m, 898w, 820s, 793m, 785m, 749m, 740w, 715s; δ_H (400 MHz, Acetone-d_6) 8.50–8.45 (2H, m, Ar *H*), 8.02–7.99 (2H, m, Ar *H*), 7.87–7.83 (1H, m, Ar *H*), 7.78–7.74 (1H, m, Ar *H*), 7.70–7.65 (2H, m, Ar *H*), 7.62–7.58 (2H, m, Ar *H*); δ_C (100 MHz, Acetone-d_6) with one C resonance missing, 165.8, 165.1, 155.4, 136.7, 134.9, 132.7, 132.6, 130.1, 129.4, 128.1; *m/z* (ESI+): 676 ([(M+H+Na)$_2$]$^+$, 9%), 507 (16), 338 (M+H+Na$^+$, 100), 337 (M+Na$^+$, 6, Calculated: 337.0265, found: 337.0244), 321 (M+Na$^+$-O, 12), 306 (M+H+Na$^+$-O_2, 5), 282 (M$^+$-O_2, 14), 256 (5).

Supplementary Materials: The following information can be downloaded online: molfile, cif file, Figure S1: ^{1}H NMR spectrum of thiadiazole **19** in acetone-d_6, Figure S2: ^{13}C NMR spectrum of thiadiazole **19** in acetone-d_6, Figure S3: IR spectrum, and Figure S4: Mass spectrum of thiadiazole **19**.

Author Contributions: E.B., A.S.K. and P.A.K. conceived the experiments; E.B. conducted the experiments; E.B. isolated and characterized compound **19**; S.B.H.P. conducted experiments with additional substrates **6b** and **6c**; A.S.K. synthesized starting materials **6a–c**; G.M.R. acquired and analyzed the SC-XRD data for compound **19**; E.B. wrote the paper; E.B., A.S.K. and P.A.K. edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The cif file for compound **19** is deposited with the Cambridge crystallographic data center [CCDC: 2168265].

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Conflicts of Interest: The authors declare no conflicts of interest.

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