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Short Note

1-Phenyl-3-tosyl-1*H*-pyrrole

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Abstract: 1-Phenyl-3-tosyl-1*H*-pyrrole was prepared, in moderate yield, by the electrophilic aromatic substitution of 1-phenyl-1*H*-pyrrole with tosyl chloride in the presence of excess zinc oxide under solvent-free conditions. A minor product was its isomer, 1-phenyl-2-tosyl-1*H*-pyrrole.

Keywords: 1-phenyl-1*H*-pyrrole; 1-phenyl-3-tosyl-1*H*-pyrrole; 1-phenyl-2-tosyl-1*H*-pyrrole; tosyl chloride; zinc; zinc oxide

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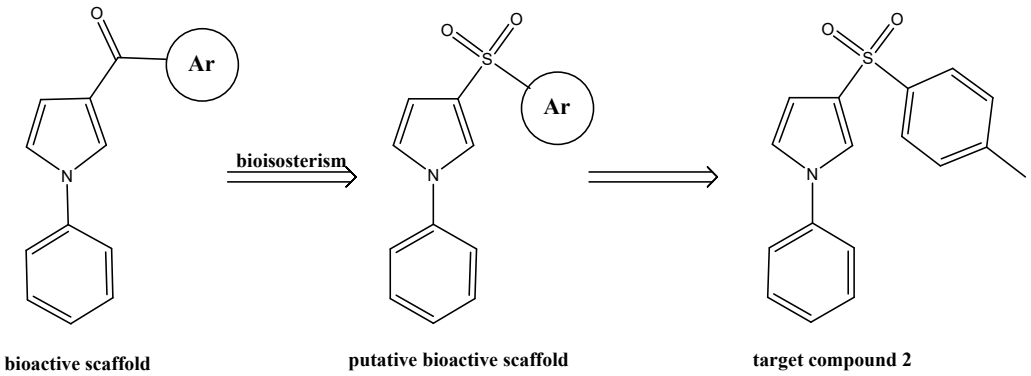
1. Introduction

The 3-aroyl-1-phenyl-1*H*-pyrrole (Scheme 1) is an important bioactive scaffold (e.g., in aldose reductase [1] and tubulin polymerization [2] inhibitors). It is also known that the sulfonyl group is used as a bioisostere for the carbonyl group in medicinal chemistry [3] and, that, sulfone is one of the forty most frequent functional groups in a number of bioactive molecules [4]. Thus, we replaced the carbonyl group with a sulfone in the above bioactive scaffold and designed 3-arylsulfonyl-1-phenyl-1*H*-pyrrole (Scheme 1) as a putative pharmacophore structure [5]. This pharmacophore could possibly lead to molecules with improved pharmacodynamic/pharmacokinetic properties. Access to these types of compounds has been previously reported by either a cycloaddition reaction of substituted munchnones with arylsulfonyl alkynes [6] or from alkynylamines and sulfinic acids via a tandem oxidative/cyclization reaction [7]. In the present work, we studied a number of methods for the direct sulfonylation of 1-phenyl-1*H*-pyrrole **1**, targeting 1-phenyl-3-tosyl-1*H*-pyrrole **2** as a representative structure.

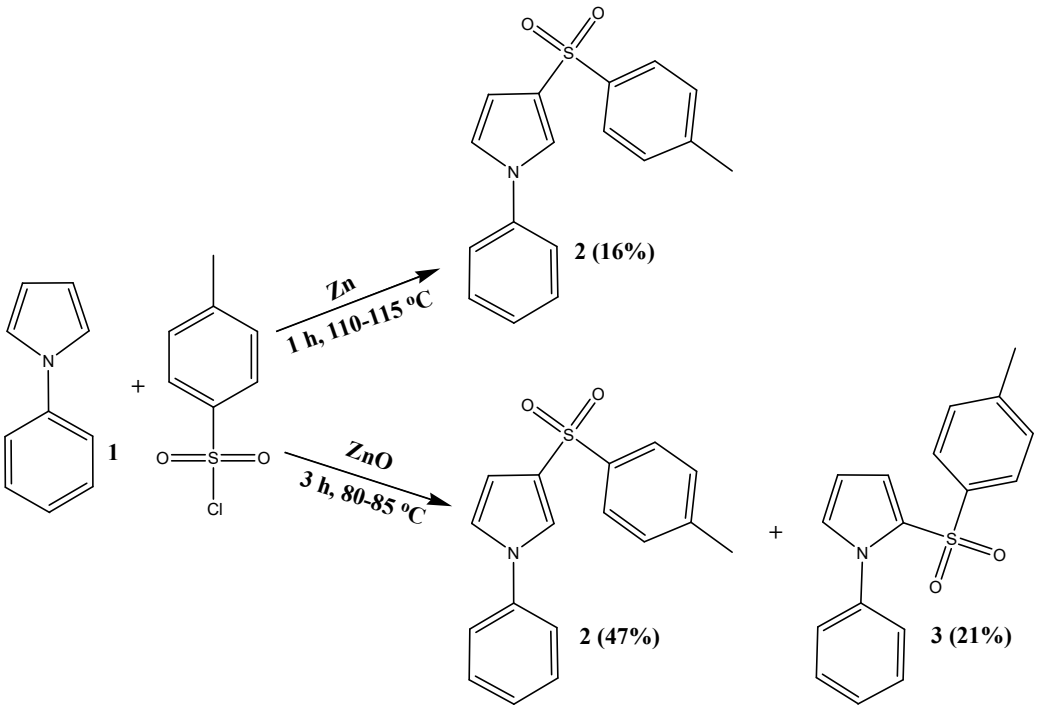


Scheme 1. Design of the target compound **2**.

2. Results and Discussion

Attempts to introduce the tosyl group via substitution of 1-phenyl-1*H*-pyrrole **1** with TsOH/PPA [8], TsCl/Zn [9] or sodium p-toluenesulfinate/I_2 [10] were unsuccessful. On the other hand, under solvent-free conditions, the reactions of **1** with TsCl/Zn [11] or TsCl/ZnO [12] gave the desired product **2** (Scheme 2). In the former reaction, the yield of **2** was low, and extensive decomposition was observed, while in the later reaction, **2** was

isolated in moderate yield along with its isomer **3**. The assignment of the structure of the two isomers (**2** and **3**) was based on the difference of the position of the signals of the hydrogen at the 4-position of the pyrrole ring in their ^{1}H NMR spectrum (see Supplementary Materials). Specifically, in the 3-isomer **2**, its signal was downfield/deshielded (6.69–6.52) compared to the 2-isomer **3** (6.38).



Scheme 2. Syntheses of the target compound **2**.

The products of the reaction catalyzed with ZnO might reflect the very mild Lewis acidity of zinc ion [13]. Overall, the yields of **2** are rather low, and we plan to try to optimize the conditions by varying the reaction's time/temperature and/or by using a combination of the zinc catalysts. On the other hand, the preferable route for compound **3** is the reported [14] photocatalytic sulfonylation.

3. Materials and Methods

All reagents were purchased from Sigma-Aldrich (Merck Group, Darmstadt, Germany) and used without further purification, except for the solvents used for flash chromatography and recrystallization. Melting points are uncorrected and were determined in open glass capillaries using a Mel-Temp II apparatus. IR spectra were taken with a Perkin-Elmer FT-IR System Spectrum BX. NMR spectra were recorded on an Agilent 500/54 (DD2) spectrometer (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR) using tetramethylsilane (TMS) as the internal standard. Mass spectra were obtained on an LCMS-2010 EV Instrument (Shimadzu) under electrospray ionization (ESI) conditions. Elemental analyses were performed at Galbraith Laboratories, Inc., Knoxville, TN. Flash column chromatography was carried out with Merck silica gel 60 (230–400 Mesh ASTM). TLC was run with Merck Silica gel/TLC-cards. Petroleum ether refers to the fraction with bp 40–60 °C.

Sulfonylation of 1-phenyl-1H-pyrrole **1** *in the presence of Zn*: **1** 143 mg (1 mmol), tosyl chloride 191 mg (1 mmol) and Zn dust 65 mg (1 mmol) were blended, and the mixture was gently stirred for 60 min at 110–115 °C under a nitrogen atmosphere. After cooling to room temperature, CH_2Cl_2 (30 mL) was added to the crude mixture, subjected to ultrasound irradiation (5 min) and filtered through celite. The concentrated filtrate was flash chromatographed (petroleum ether/ethyl acetate 85/15 to 80/20) on silica gel to yield 46 mg (16%) of 1-phenyl-3-tosyl-1*H*-pyrrole **2**. An analytical sample was prepared by

recrystallization from CH_2Cl_2/petroleum ether; R_f = 0.46, petroleum ether/ethyl acetate 8:2; mp 160–162 °C; IR (KBr): 1598, 1515, 1301 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.13–8.04 (m, 1H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.52–7.46 (m, 3H), 7.44–7.30 (m, 3H), 6.69–6.52 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 143.74, 140.85, 138.99, 130.36, 130.15, 127.52, 127.10, 126.90, 123.37, 122.60, 120.91, 110.16, 21.421; MS (ESI): *m/z* 319.85 $[M + Na]^+$, 351.80 $[M + Na + MeOH]^+$, 616.85 $[2M + Na]^+$; Anal. calcd. for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.74; H, 4.56; N, 4.35.

Sulfonylation of 1-phenyl-1H-pyrrole **1** *in the presence of ZnO*: **1** 143 mg (1 mmol), tosyl chloride 229 mg (1.2 mmol) and ZnO fine powder 244 mg (3 mmol) were blended, and the mixture was gently stirred for 12 h at 80–85 °C under a nitrogen atmosphere. After cooling to room temperature, CH_2Cl_2 (30 mL) was added to the crude mixture, subjected to ultrasound irradiation (5 min) and filtered through celite. The concentrated filtrate was flash chromatographed (petroleum ether/ethyl acetate 85/15 to 80/20) on silica gel to yield, in order:

(a) 1-phenyl-2-tosyl-1*H*-pyrrole **3** 62 mg (21%). An analytical sample was prepared by recrystallization from petroleum ether; R_f = 0.69, petroleum ether/ethyl acetate 8:2; mp 116–118 °C; lit. [14] 99–101 °C; IR (KBr): 1592, 1491, 1316 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.42 (t, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 4H), 7.22 (dd, *J* = 3.9, 1.80 Hz, 1H), 7.12 (t, *J* = 9 Hz, 4H), 6.88 (t, *J* = 2.2 Hz, 1H), 6.33 (dd, *J* = 3.6, 3.0 Hz, 1H), 2.37 (s, 3H), consistent with the reported [14] ^1H NMR ($CDCl_3$) data; ^1H NMR (DMSO-d_6): δ 7.45 (t, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.25–7.19 (m, 5H), 7.11 (dd, *J* = 3.9, 1.8 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 2H), 6.38 (dd, *J* = 3.8, 2.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6): 144.18, 138.86, 138.04, 131.43, 130.25, 129.99, 129.30, 129.01, 127.88, 127.35, 119.42, 109.36, 21.45, consistent with the reported [14] ^{13}C NMR ($CDCl_3$) data; MS (ESI): *m/z* 319.85 $[M + Na]^+$, 351.80 $[M + Na + MeOH]^+$, 616.90 $[2M + Na]^+$.

(b) 1-phenyl-3-tosyl-1*H*-pyrrole **2** 140 mg (47%).

Supplementary Materials: The following are available online. Figure S1: IR (KBr) spectrum of compound 2, Figure S2: 1H NMR (500 MHz, DMSO-d6) spectrum of compound 2, Figure S3: 13C-NMR (125 MHz, DMSO-d6) spectrum of compound 2, Figure S4: MS (ESI) spectrum of compound 2.

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Data Availability Statement: The data presented in this study are available in this article.

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

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