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Synthesis of a New Spiro System: 1-Oxa-7-thia-4-azaspiro[4.5]decane 7,7-Dioxide

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Abstract—Dihydro-2*H*-1λ^6-thiopyran-1,1,3(4*H*)-trione reacted with N-substituted 2-aminoethanols to give derivatives of a new spiro system, 1-oxa-7λ^6-thia-4-azaspiro[4.5]decane-7,7-diones. No spirocyclic product was obtained by the reaction with unsubstituted 2-aminoethanol, but the corresponding enamine was formed as in the reactions with other primary amines.

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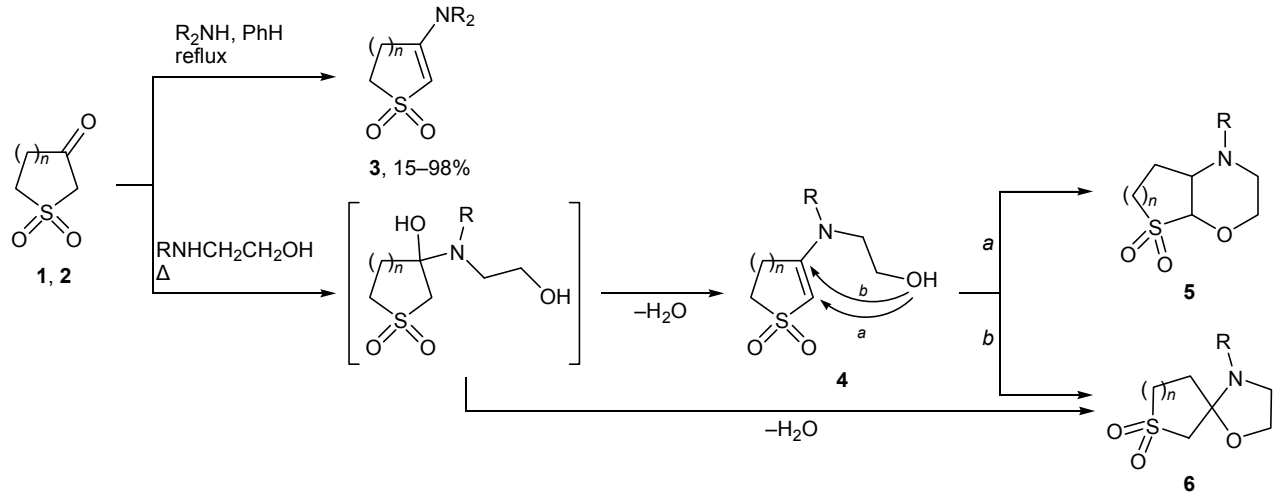
Cyclic and acyclic β-keto sulfones are valuable starting compounds for the synthesis of many heterocycles such as pyridines, pyrazoles, benzothiazoles, dihydropyridines, dihydropyridazines, pyrimidinones, and thiophenes [1, 2]. β-Keto sulfones (e.g., compounds **1** and **2**) are known to react with various primary and secondary amines to give the corresponding enamines **3** [3–6]. Surprisingly, we have found no published data on reactions of any cyclic or acyclic β-keto sulfones with vicinal amino alcohols, though this reaction attracts considerable interest due to the possibility of obtaining compounds like **4** or products of their further heterocyclizations, fused morpholines **5** and spiro oxazolidines **6** (Scheme 1). Spirocyclic biologically active compounds are just those that play a particular role in the drug discovery [7].

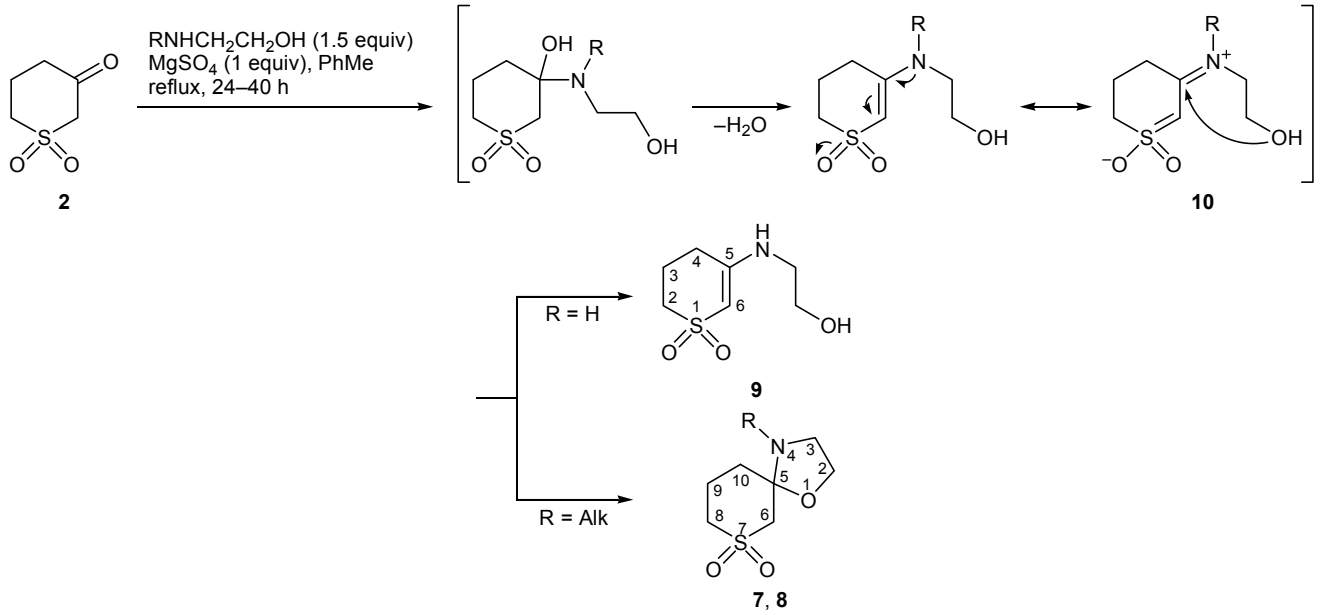
All our attempts to synthesize any of compounds **4**–**6** by reaction of five-membered keto sulfone **1** [8] with N-substituted 2-aminoethanols were unsuccessful. In order to reduce the overall steric strain and increase conformational mobility of the system we used six-membered β-keto sulfone **2** [9]. It was converted in high yields to 1-oxa-7λ^6-thia-4-azaspiro[4.5]decane-7,7-diones **7** and **8** which were identified on the basis

Scheme 1.



R = Alk, Ar; **1**, *n* = 1; **2**, *n* = 2.

Scheme 2.

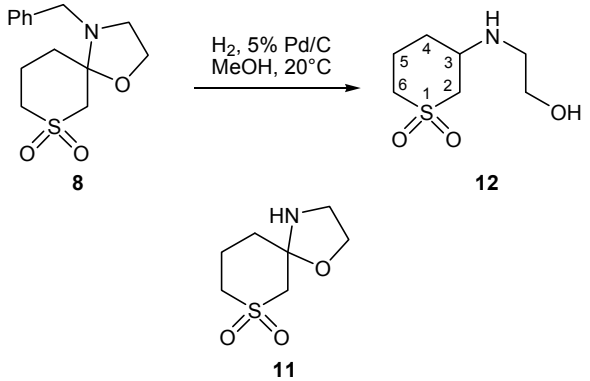


7, R = Me; **8**, R = $PhCH_2$.

of the ^1H and ^{13}C NMR data, including COSY, NOESY, and HSQC experiments. The reaction of **2** with unsubstituted 2-aminoethanol afforded exclusively enamine **9** (Scheme 2). The different reactivities of amino alcohols can be readily rationalized assuming the existence of resonance structure **10** which possess an N^+=C–C=S–O^- fragment. The more stable is structure **10**, the higher the probability of its spirocyclization. Presumably, unlike alkyl groups, weak positive inductive effect of hydrogen on the nitrogen atom does not ensure sufficient stabilization.

All new NH-heterocyclic systems are of significant interest for their further functionalization at the nitrogen atom [10]. Taking into account that we failed to obtain NH-containing spiro compound **11** from keto sulfone **2** and 2-aminoethanol, we tried to synthesize it

Scheme 3.



by debenzylation of **8**. However, the hydrogenation of **8** over 5% Pd/C was accompanied by reductive cleavage of the oxazolidine ring with the formation of amino alcohol **12** (Scheme 3). The structure of **12** was confirmed by the absence of signal at about δ_C 94 ppm (spiro carbon atom) in the ^{13}C NMR spectrum.

It is known that sulfones [1, 11–13], as well as fluorine-containing derivatives [14–16], are promising compounds for medicinal and agricultural chemistry. Therefore, we extended the series of enamines with a thiopyran 1,1-dioxide fragment. As in the synthesis of spiro compounds **7** and **8**, enamines **13**–**17** were isolated with considerably higher purity and yields when the reactions were carried out using 1.5-equiv of the amine. Because of low boiling point (37°C) and high volatility of 2,2,2-trifluoroethanamine, its amount was increased to 10 equiv to ensure its excess concentration in the reaction mixture, and the reaction was carried in a hermetically closed thick-walled glass reactor (Scheme 4).

The ^1H NMR spectra of **7** and **8** clearly indicated the formation of spiro oxazolidines: there were no signals in the region δ 4.0–14.0 ppm (except for the aromatic proton signals), which is impossible for enamine structures like **4**. The olefinic proton on C^6 in the enamine structure should resonate in the region δ 4.86–5.36 ppm (cf. the data for compounds **13**–**17**). Alternative structures like **5** should give rise to signals at δ 4.0–5.5 ppm due to protons on the bridgehead carbon atoms [17]. The structure of *N*-benzyl deriva-