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SYNTHESIS OF SOME HETEROCYCLIC SPIROCOMPOUNDS

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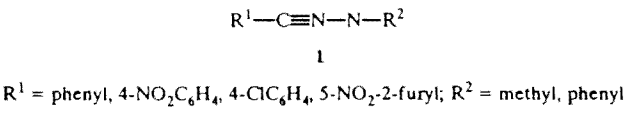
1,3-Dipolar cycloaddition reactions of methylenepyrrolidinones with nitrilimines or nitrones resulted in regio- and stereoselective formation of respective spiropyrazolines or spiroisovazolidines.

The field of 1,3-dipolar cycloaddition chemistry developed dramatically during the past 25 years and became a generally useful method for the synthesis of five-membered heterocyclic systems.

As a part of our study directed towards the utilization of heterocyclic compounds as dipolarophiles in 1,3-dipolar cycloaddition reactions, we report some cycloadditions of C-aryl and C-heteroaryl nitrilimines **1** and nitrones **2** to 1-substituted 3,3-methylene-5,5-dimethyl-2-pyrrolidinones (**3**). Our attention to this type of reaction was attracted by the recent observation of excellent herbicidal activity of some spirocyclic lactams [1], coupled with the absence of toxicity to microorganisms, and also by the fact that many of the C-(5-nitro-2-furyl)-N-substituted nitrones possess broad spectrum of *in vitro* antibacterial activity [2, 3].

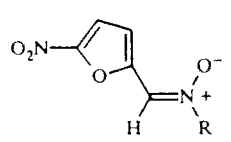
1,3-Dipolar cycloadditions of nitrilimines **1** to methylenepyrrolidinones **3** were performed by *in situ* techniques. The method of Rai and Hassner [4] turned out to be the most versatile and perfectly suited for application on furan derivatives [5, 6]. The nitrilimines have been generated from appropriate aldehyde hydrazones by treatment of chloramine T trihydrate (N-chloro-N-sodio-4-methylbenzenesulfonamide, CAT). Generally, the cycloaddition was carried out by heating an equimolecular mixture of a hydrazone, methylenepyrrolidinone **3**, and chloramine T in ethanol (or methanol) under reflux. The reaction course was monitored by thin-layer chromatography.

1-R-Substituted 3,3-methylene-5,5-dimethyl-2-pyrrolidinones (**3b-d**) were prepared from the parent derivative **3a** using alkylation in the presence of appropriate base [7]. The corresponding 1-(1-methyl)ethenyl derivative **3d** is formed as a by-product by the preparation of **3a** involving treatment of 2,2,6,6-tetramethyl-4-piperidone in chloroform with 50% aqueous NaOH under catalysis by TEBA [8].

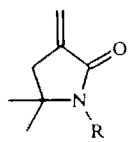


1

R^1 = phenyl, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 5-NO_2-2-furyl; R^2 = methyl, phenyl



2a, b



3a–d

2a R = methyl, b R = phenyl; 3 a R = H, b R = $COCH_3$, c R = BOC, d R = CH_2=$C(CH_3)$

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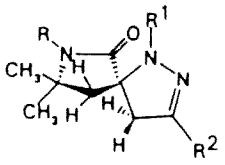
Cycloadditions of C-aryl- and C-furyl-N-methyl, resp. -N-phenyl nitrilimines **1** to the exocyclic double bond of **3** proceeded with complete regio- and diastereoselectivity, giving only spiropyrazolines **4** (7-R-substituted 6-oxo-8,8-dimethyl-1,2,7-triazaspiro[4,4]non-2-enes) in very good yields. The corresponding regioisomer **5** has not been detected in a crude reaction mixture by NMR spectroscopy. The assignment of the regiochemistry in pyrazolines **4** was made on the basis of ^{1}H and ^{13}C NMR data.



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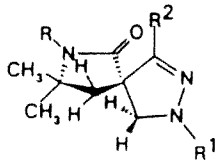

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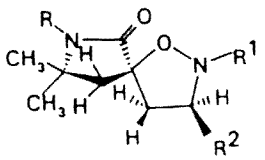
We have recently demonstrated that diaryl nitrones react regioselectively with methylenepyrrolidinones **3** to give a mixture of diastereomeric spirocycloadducts **6** and **7**, in which **6** always dominates [9, 10]. We enlarged the scale of used 1,3-dipoles also to C-(5-nitro-2-furyl)-N-methyl, resp. -N-phenyl nitrones **2**. They have been prepared from 5-nitro-2-furaldehyde by the usual procedure [11]. A single isomer was obtained in all cases and the expected Z configuration was confirmed by nuclear Overhauser effect difference spectroscopy (NOEDS), which showed an enhancement of the N-methyl signal in **2a** upon irradiation of the azomethine hydrogen, as well as an enhancement of the azomethine proton signal upon irradiation of the methyl group.

Cycloadditions of nitrones **2** to methylenepyrrolidinone **3a** were performed in boiling toluene. Experiments with N-methyl nitrone **2a** were unsuccessful; also, after 60 hours reflux, we isolated only the starting materials and small amounts of furan tars from the reaction mixture. N-Phenyl analogue **2b** reacted readily with **3a**, giving exclusively the isoxazolidine **6** as the single product in excellent yield. The corresponding regioisomers **8** and **9** were not detected in the crude reaction mixture.



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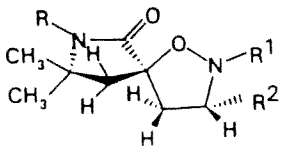

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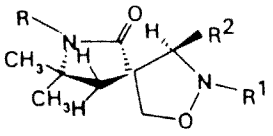

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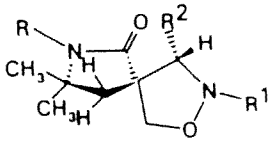

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The diastereomeric isoxazolidines **6** and **7** can be formed via different two-plane oriented complexes (*exo* or *endo* arrangement between N—Ph and C=O groups). Cycloaddition of Z-nitrone **2** via *exo* transition state results in the formation of isoxazolidine **6**. An examination of both transition states reveals that repulsions between the phenyl group on nitrogen and substituents on **3** are minimized in the *exo* transition state.

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