Use of Some Aryl and Heteroaryl Nitrilimines and Nitrones in the Synthesis of Spiroheterocycles

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Dedicated to Professor Alžbeta Krutošíková on the occasion of her 70th birthday.

1,3-Dipolar cycloadditions of *C*-(5-nitro-2-furyl)-*N*-methyl nitrilimine (**2a**), *C*-(5-nitro-2-furyl)-*N*-phenyl nitrilimine (**2b**), *C*-4-nitrophenyl-*N*-methyl nitrilimine (**2c**) and *C,N*-diphenyl nitrilimine (**2d**) with 1-R-substituted 3,3-methylene-5,5-dimethylpyrrolidin-2-ones (**1a-d**) where R is H, acetyl, 1,1-dimethylethoxycarbonyl and 1-methylethenyl proceed with complete regioselectivity in good yields to afford 1,3,7-trisubstituted-6-oxo-8,8-dimethyl-1,2,7-triazaspiro[4,4]non-2-enes (**5a-g**) exclusively. Cycloaddition of *C*-(5-nitro-2-furyl)-*N*-phenylnitrone (**3b**) to the exocyclic double bond of the dipolarophile **1a** proceeds to 2-phenyl-3-(5-nitro-2-furyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro[4,4]nonane (**7**) with complete regio- and stereoselectivity.

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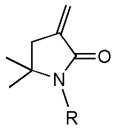
The field of 1,3-dipolar cycloaddition chemistry has developed dramatically during the past twenty five years and became a generally useful method for five-membered heterocyclic ring synthesis. As a part of our study directed towards the utilization of heterocyclic compounds as dipolarophiles in 1,3-dipolar cycloadditions, we have reported some cycloadditions of arylnitrile oxides and nitrones to 1-R-substituted 3,3-methylene-5,5-dimethylpyrrolidin-2-ones (**1a-d**) where R is H, acetyl, 1,1-dimethylethoxycarbonyl and 1-methylethenyl [1-3]. Since the reaction of the dipolarophiles **1a-d** with 1,3-dipoles could be of some mechanistic interest regarding the peculiarity of the regioselectivity pattern in electron-defficient alkenes in the 1,3-dipolar cycloadditions, we enlarged the scale of used dipoles with some heteroaryl and aryl substituted nitrilimines. Our attention to this type of reaction was also attracted by the observation of the excellent herbicidal activity of some spiro cyclic lactams [4] coupled with the absence of toxicity to microorganisms and also by the fact, that many of *C*-(5-nitro-2-furyl)-*N*-substituted nitrones posseses broad spectrum *in vitro* antibacterial activity [5,6]. In the present communication, we report the investigation of the regio- and stereoselectivity of reactions of *C*-(5-nitro-2-furyl)-*N*-methyl nitrilimine (**2a**), *C*-(5-nitro-2-furyl)-*N*-phenyl nitrilimine (**2b**), *C*-4-nitrophenyl-*N*-methyl nitrilimine (**2c**), *C,N*-diphenyl nitrilimine (**2d**) [7], *C*-(5-nitro-2-furyl)-*N*-methylnitrone (**3a**) and *C*-(5-nitro-2-furyl)-*N*-phenylnitrone (**3b**) with 3,3-methylene-5,5-dimethylpyrrolidin-2-ones (**1a-d**).

1,3-Dipolar cycloadditions of nitrilimines **2a-d** to methylenepyrrolidinones **1a-d** were performed by *in situ* technique. The method of Rai and Hassner [8] turned out to be the most versatile and perfectly suited also for the application on furan derivatives [9,10]. The nitrilimines **2a-d** have been generated from appropriate aldehyde hydrazones **4** 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 **1a-d**, and chloramine-T in ethanol or methanol under reflux. 1,3-Dipolar cycloadditions of *C*-(5-nitro-2-furyl)-*N*-methyl nitrilimine (**2a**), *C*-(5-nitro-2-furyl)-*N*-phenyl nitrilimine (**2b**), *C*-4-nitrophenyl-*N*-methyl nitrilimine (**2c**) and *C,N*-diphenyl nitrilimine (**2d**) to the exocyclic double bond of 1-R-substituted 3,3-methylene-5,5-dimethylpyrrolidin-2-ones (**1a-d**) where R is H, acetyl, 1,1-dimethylethoxycarbonyl and 1-methylethenyl proceed with complete regioselectivity in good yields to afford 1,3,7-trisubstituted-6-oxo-8,8-dimethyl-1,2,7-triazaspiro[4,4]non-2-enes (**5a-g**) exclusively. The corresponding 4-substituted regioisomer **6** has not been detected in crude reaction mixture by ^{1}H NMR spectroscopy. The assigment of the regiochemistry in spiropyrazolines **5a-g** was made on the basis of ^{1}H and ^{13}C NMR spectral data.

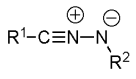
It is noteworthy to mention that the cycloaddition of *C*-(5-nitro-2-furyl)-*N*-methyl nitrilimine (**2a**) with 1-acetyl-3,3-methylene-5,5-dimethylpyrrolidin-2-one (**1b**) provided a mixture of two spiropyrazolines **5b** and unexpected **5a** in 68% and 21% yields, respectively. Furthermore, no thermal interconversion among cycloadducts **5a** and **5b** occurred in refluxing ethanol, thus indicating that the competitive deacetylation of **1b** proceeded under the cycloaddition conditions to give **1a**. Surprisingly, a complete deacetylation is observed in the cycloaddition of *C*-4-nitrophenyl-*N*-methyl nitrilimine (**2c**) with 1-acetyl-3,3-methylene-5,5-dimethylpyrrolidin-2-one (**1b**); reaction leads to formation of spiropyrazoline **5e** exclusively.

In our previous work we have demonstrated that diaryl nitrones react regioselectively with methylenepyrrolidinone **1a** giving the mixture of diastereomeric spirocycloadducts **7** and **8** (instead of 5-nitro-2-furyl is phenyl), in

Scheme 1



1



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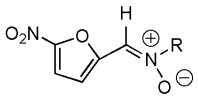
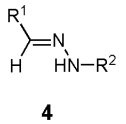


3

1a R = H
1b R = $COCH_3$
1c R = BOC
1d R = 1-methylethenyl

2a R^1 = 5-NO_2-2-furyl, R^2 = Me
2b R^1 = 5-NO_2-2-furyl, R^2 = Ph
2c R^1 = 4-NO_2-phenyl, R^2 = Me
2d R^1 = R^2 = Ph

3a R = Me
3b R = Ph



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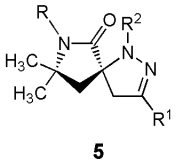
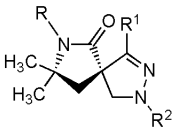


5

	R	R^1	R^2
5a	H	5-NO_2-2-furyl	methyl
5b	CH_3CO	5-NO_2-2-furyl	methyl
5c	BOC	5-NO_2-2-furyl	methyl
5d	H	5-NO_2-2-furyl	phenyl
5e	H	4-NO_2-phenyl	methyl
5f	CH_2=C(CH_3)	5-NO_2-2-furyl	methyl
5g	H	phenyl	phenyl



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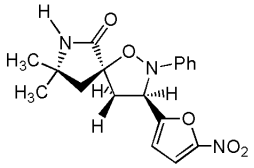

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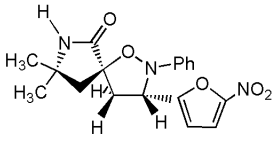

8

which **6** always dominates [2,3]. We enlarged the scale of used 1,3-dipoles also to *C*-(5-nitro-2-furyl)-*N*-methylnitrone (**3a**) and *C*-(5-nitro-2-furyl)-*N*-phenylnitrone (**3b**). Nitrones **3a** and **3b** have been prepared from 5-nitro-2-furancarbaldehyde by the usual procedure [12]. A single isomer was obtained in both cases and the expected *Z* configuration was confirmed by nuclear Overhauser effect difference spectroscopy (NOEDS). An enhancement of the *N*-methyl signal in **3a** was shown upon irradiation of the azomethine hydrogen as well as enhancement of the azomethine proton signal upon irradiation of the methyl group. Cycloadditions of nitrones **3a,b** to methylenepyrrolidinone **1a** were performed in boiling toluene. Experiments with *N*-methyl nitrone **3a** were totally unsuccesfull. It is noteworthy to mention that at reflux in toluene no cycloaddition has been observed; after 60 hours only the unreacted starting materials were detected. On the other hand, *N*-phenyl analogue **3b** reacted more readily with **1a**; purification by flash chromatography allowed the isolation of the pure diastereoisomer **7** as the sole product in 46% yield. This fact can be explained by FMO analysis of AM1 calculated frontier orbitals of **1a** [3]. Inspection of energy levels of **1a** showed that the cycloaddition to **1a** is governed by the LUMO dipole and therefore the *N*-phenyl group lowered the HOMO and LUMO energies of the nitrone **3b**, compared with the nitrone **3a** and should activate the nitrone part of **3b** for a 1,3-dipolar cycloaddition reaction with pyrolidinone **1a**. The corresponding diastereoisomer **8** could not been detected in the crude reaction mixture. Cycloaddition of *Z*-nitrone **3b** *via exo* transition state results in the formation of isoxazolidine **7**.

EXPERIMENTAL

Melting points were determined on Kofler hot plate apparatus, the IR spectra were taken with Philips analytical PU 9800 FTIR spectrometer in KBr pellets. The ^{1}H and ^{13}C nmr spectra of deuterochloroform solutions were recorded on a Varian VXR 300 spectrometer, chemical shifts are reported in ppm from tetramethylsilane as internal standard, coupling constants in Hz. Methyl, methylene and methine groups, and quaternary carbons, were discriminated in the ^{13}C nmr spectra by DEPT experiments. Mass spectral data were recorded on AEI spectrometer MS 902 S with direct inlet and ionizing energy of 70 eV, capture current 100 μA and temperature of ionizing chamber 80 - 215 °C. Elemental analyses were caried out on Carlo Erba CHNS-O 1108 apparatus and were in good accord with theoretical data. All

reagents were purified and dried if necessary prior to use. The reaction course was monitored by TLC. TLC analyses were carried out with Lachema UV_{254} silica gel plates.

1-R-Substituted 3,3-methylene-5,5-dimethyl-2-pyrrolidinones **1a-d** were prepared from the parent derivative **1a** by applying an alkylation in the presence of appropriate base [11]. The corresponding 1-(1-methylethenyl) derivative **1d** is formed as a by-product by the preparation of **1a** involving treatment of 2,2,6,6-tetramethyl-4-piperidone in chloroform with 50% aqueous NaOH under catalysis by TEBA [3]. Nitrones **3a**,**b** have been prepared from 5-nitro-2-furancarbaldehyde by the usual procedure [12].

General Procedure for the Reaction of Nitrilimines (**2a-d**) with 1-R-Substituted 3,3-Methylene-5,5-dimethylpyrrolidin-2-ones (**1a-d**).

The hydrazones **4a-d** (2 mmoles) and appropriate methylenepyrrolidinones **1a-d** (2 mmoles) and Chloramine-T (CAT) (3 mmoles) were heated under reflux in methanol or ethanol (40 ml) for 1-6 hours (monitored by TLC). After evaporation of solvent *in vacuo*, the pure products **5a-g** were isolated by column chromatography using chloroform or hexane-ethyl acetate (1:1) as eluent.

1-Methyl-3-(5-nitro-2-furyl)-6-oxo-8,8-dimethyl-1,2,7-triazaspiro[4,4]non-2-ene (**5a**).

This compound was obtained as red needles (ethanol), (86%), mp 275-277°; ir: CO 1693, CN 1581 cm^{-1}; ^1H nmr: δ 1.38 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.15 (d, 1H, 9-Ha, J = 14.4 Hz), 2.37 (d, 1H, 9-Hb), 3.11 (s, 3H, N-CH_3), 3.23 (d, 1H, 4-Ha, J = 16.8 Hz), 3.69 (d, 1H, 4-Hb), 5.85 (s, 1H, NH), 6.76 (d, 1H, J = 3.9 Hz, furyl protons), 7.36 (d, 1H, furyl protons); ^{13}C nmr: δ 30.27 (CH_3), 30.51(CH_3), 35.40 (N-CH_3), 44.79 (C-4), 45.58 (C-9), 53.01 (C-8), 76.33 (C-5), 109.26, 114.38, 159.53 (furyl carbons), 151.43 (C-3), 172.63 (CO); ms: m/z 293 $(M+1)^+$ (15), 292 (M+ 92), 247 (32), 234 (19), 232 (29), 207 (82), 206 (30), 86 (76), 58 (100), 42 (24).

Anal. Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.40; H, 5.51; N, 19.16. Found: C, 53.61; H, 5.32; N, 19.28.

1-Methyl-3-(5-nitro-2-furyl)-6-oxo-7-acetyl-8,8-dimethyl-1,2,7-triazaspiro[4,4]non-2-ene (**5b**).

This compound was obtained as dark yellow needles (ethanol), (68%), mp 141-143°; ir: CO 1734, 1707, CN 1589 cm^{-1}; ^1H nmr: δ 1.56 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 2.09 (d, 1H, 9-Ha, J = 11.1 Hz), 2.29 (d, 1H, 9-Hb), 2.47 (s, 3H, $COCH_3$), 3.06 (s, 3H, N-CH_3), 3.25 (d, 1H, 4-Ha, J = 13.5 Hz), 3.63 (d, 1H, 4-Hb), 6.76 (d, 1H, J = 3.1 Hz, furyl protons), 7.32 (d, 1H, furyl protons); ^{13}C nmr: δ 26.2 (CH_3), 27.1 (CH_3), 28.9 (CH_3), 35.3 (N-CH_3), 44.87 (C-4), 45.0 (C-9), 59.45 (C-8), 73.0 (C-5), 109.39, 114.3, 134.96 (furyl carbons), 151.0 (C-3), 171.9 (CO), 172.9 (CO); ms: m/z (M+ 334, 91%).

Anal. Calcd. for $C_{15}H_{18}N_4O_5$: C, 53.89; H, 5.43; N, 16.76. Found: C, 53.41; H, 5.35; N, 16.48.

1-Methyl-3-(5-nitro-2-furyl)-6-oxo-7-(1,1-dimethylethoxycarbonyl)-8,8-dimethyl-1,2,7-triazaspiro[4,4]non-2-ene (**5c**).

This compound was obtained as orange plates (methanol), (84%), mp 167-169°; ir: CO 1778, 1730, CN 1587 cm^{-1}; ^1H nmr: δ 1.55 (s, 9H, 3×CH_3), 1.56 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.09 (d, 1H, 9-Ha, J = 13.7 Hz), 2.27 (d, 1H, 9-Hb), 3.08 (s, 3H, N-CH_3), 3.24 (d, 1H, 4-Ha, J = 16.8 Hz), 3.68 (d, 1H, 4-Hb), 6.76 (d, 1H, J = 3.9 Hz, furyl protons), 7.36 (d, 1H, furyl protons); ^{13}C nmr: δ 26.29 (CH_3), 28.0 (CH_3), 29.3 (CH_3), 35.37 (N-CH_3), 44.75 (C-4), 44.84 (C-9), 58.6 (C-8), 73.1 (C-5), 83.9 (C-*t*Bu), 109.2, 114.4, 134.9 (furyl carbons), 149.8 (OCO), 151.3 (C-3), 170.9 (CO); ms: m/z 392 (M+, 76).

Anal. Calcd. for $C_{18}H_{24}N_4O_6$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.71; H, 6.56; N, 14.00.

1-Phenyl-3-(5-nitro-2-furyl)-6-oxo-8,8-dimethyl-1,2,7-triazaspiro[4,4]non-2-ene (**5d**).

This compound was obtained as dark orange plates (ethanol), (74%), mp 255-256°; ir: CO 1709, CN 1595 cm^{-1}; ^1H nmr: δ 1.36 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.07 (d, 1H, 9-Ha, J = 14.1 Hz), 2.55 (d, 1H, 9-Hb), 3.49 (d, 1H, 4-Ha, J = 17.1 Hz), 3.76 (d, 1H, 4-Hb), 6.56 (s, 1H, NH), 6.92 (d, 1H, J = 3.9 Hz, furyl protons), 7.02 (dd, 1H, phenyl protons), 7.20-7.31 (m, 4H, phenyl protons), 7.42 (d, 1H, furyl protons); ^{13}C nmr: δ 30.0 (CH_3), 30.8 (CH_3), 46.40 (C-9), 53.4 (C-4), 58.5 (C-8), 73.1 (C-5), 109.39, 114.3(furyl carbons), 116.5, 122.3, 129.3,135.5, 141.4 (phenyl carbons), 151.0 (C-3), 174.3 (CO); ms: m/z 354 (M+, 87).

Anal. Calcd. for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 61.20; H, 5.36; N, 15.55.

1-Methyl-3-(4-nitrophenyl)-6-oxo-8,8-dimethyl-1,2,7-triazaspiro[4,4]non-2-ene (**5e**).

This compound was obtained as dark red needles (ethanol), (66%), mp 248-249°; ir: CO 1705, CN 1591 cm^{-1}; ^1H nmr: δ 1.38 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.13 (d, 1H, 9-Ha, J = 14.4 Hz), 2.39 (d, 1H, 9-Hb), 3.11 (s, 3H, N-CH_3), 3.18 (d, 1H, 4-Ha, J = 16.3 Hz), 3.65 (d, 1H, 4-Hb), 6.25 (s, 1H, NH), 7.66 (d, 2H, J = 9.0 Hz, phenyl protons), 8.17 (d, 2H, phenyl protons); ^{13}C nmr: δ 30.3 (CH_3), 30.5 (CH_3), 35.5 (N-CH_3), 45.53 (C-9), 45.76 (C-4), 52.9 (C-8), 74.2 (C-5), 123.8, 125.5, 138.86, 143.1(phenyl carbons), 146.8 (C-3), 173.5 (CO); ms: m/z 302 (M+, 92).

Anal. Calcd. for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.73; H, 5.93; N, 18.42.

1-Methyl-3-(5-nitro-2-furyl)-6-oxo-7-(1-methylethenyl)-8,8-dimethyl-1,2,7-triazaspiro[4,4]non-2-ene (**5f**).

This compound was obtained as dark orange needles (methanol), (73%), mp 132-134°; ir: CO 1691, CN 1585 cm^{-1}; ^1H nmr: δ 1.40 (s, 6H, 2×CH_3), 1.97 (s, 3H, CH_3), 2.19 (d, 1H, 9-Ha, J = 13.8 Hz), 2.35 (d, 1H, 9-Hb), 3.09 (s, 3H, N-CH_3), 3.22 (d, 1H, 4-Ha, J = 16.8 Hz), 3.66 (d, 1H, 4-Hb), 4.91 (s, 1H, vinylic protons), 5.24 (s, 1H, vinylic protons), 6.75 (d, 1H, J = 3.9 Hz, furyl protons), 7.37 (d, 1H, H furyl protons); ^{13}C nmr: δ 21.95 (CH_3), 28.56 (CH_3), 29.11 (CH_3) , 35.24 (N-CH_3), 44.52, 45.71 (C-4 and C-9), 58.74 (C-8), 73.11 (C-5), 109.09, 114.55, 115.90, 134.84, 139.24 (furyl and vinylic carbons), 151.7 (C-3), 169.88 (CO); ms: m/z 332 (M+, 89).

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.81; H, 6.06; N, 16.85. Found: C, 57.32; H, 6.46; N, 16.46.

1,3-Diphenyl)-6-oxo-8,8-dimethyl-1,2,7-triazaspiro[4,4]non-2-ene (**5g**).

This compound was obtained as dark red plates (methanol), (65%), mp 214-215°; ir: CO 1702 (C=O), CN 1590 cm^{-1}; ^1H nmr: δ 1.24 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.11(d, 1H, 9-Ha, J= 13.8 Hz), 2.52 (d 1H, 9-Hb), 3.43 (d, 1H, 4-Ha, J = 16.2 Hz), 3.82 (d, 1H, 4-Hb), 6.89 (s, 1H, NH), 7.17 - 7.77 (m, 10H, phenyl protons).

Anal. Calcd. for $C_{20}H_{21}N_3O$: C, 75.20; H, 6.62; N, 13.15. Found: C, 74.91; H, 6.46; N, 12.86.

2-Phenyl-3-(5-nitro-2-furyl)-6-oxo-8,8-dimethyl-1-oxa-2,7-diazaspiro[4,4]nonane (**7**).

A solution of *C*-(5-nitro-2-furyl)-*N*-phenylnitrone (**3b**) (1.16 g, 5 mmoles) and 3,3-methylene-5,5-dimethyl-pyrrolidin-2-one (**1a**) (0.60 g, 5 mmoles) in dry toluene (30 ml) was heated under reflux for 30 hours (monitored by TLC). Evaporation of the solvent *in vacuo* and chromatogaphy on silica gel using chlorofom as eluent gave the corresponding cycloadduct **7** as light yellow plates (ethanol), (46%), mp 216-217°; ^{1}H nmr: δ 1.30 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.07 (d, 1H, 9-Hb, J = 14.4 Hz), 2.41 (d, 1H, 9-Ha), 2.59 (dd, 1H, 4-Hb, J = 12.8 and 6.4 Hz), 3.19 (dd, 1H, 4-Ha), 5.12 (dd, 1H, 3-H), 6.25(s, 3H, N-CH_3), 6.56 (d, 1H, furyl protons, J = 3.2 Hz), 7.26 (d, 1H, furyl protons), 7.02-7.35 (m, 5H, phenyl protons).

Anal. Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.72; H, 5.22; N, 11.81.

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