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Regio- and Stereoselective 1,3-Dipolar Cycloaddition of Arylnitrile Oxides to 5-Acetoxy-2(5*H*)-furanone

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Summary. Arylnitrile oxides undergo regio- and stereo-specific 1,3-dipolar cycloaddition reactions with 5-acetoxy-2(5*H*)-furanone. In each case a single product **3a–3g** results from an *anti* approach to the 5-acetoxy substituent, the oxygen of the 1,3-dipole being attached to C-4 of furan. Under similar conditions 5-benzoyloxy-2(5*H*)-furanone yields **3h–3i**. The structures of the adducts were determined by ^{1}H- and ^{13}C-NMR spectroscopy.

Keywords. 1,3-Dipolar cycloaddition of nitrile oxides; 5-Acetoxy- and 5-benzoyloxy-2(5*H*)-furanone; Regio- and stereoselective 1,3-dipolar cycloaddition.

Regio- und stereoselektive 1,3-dipolare Cycloaddition von Arylnitriloxiden mit 5-Acetoxy-2(5*H*)-furanon

Zusammenfassung. Arylnitriloxide reagieren mit 5-Acetoxy-2(5*H*)-furanon in einer regio- und stereoselektiven 1,3-dipolaren Cycloaddition. In jedem der untersuchten Fälle ergaben sich die einheitlichen Produkte **3a–3g** als Folge einer *anti*-Annäherung an den 5-Acetoxysubstituenten, wobei der Sauerstoff des 1,3-Dipols an das C-4 des Furans addiert. Unter ähnlichen Bedingungen ergab 5-Benzoyloxy-2(5*H*)-furanon die Produkte **3h–3i**. Die Strukturen der Addukte wurden mittels ^{1}H- und ^{13}C-NMR bestimmt.

Introduction

2-Isoxazolines (4,5-dihydroisoxazoles) have recently become established [1] as convenient and versatile sources of functionality present in natural products. There is therefore renewed interest in their synthesis via 1,3-dipolar cycloaddition of nitrile oxides to alkenes, with particular attention being focused on the factors influencing stereo- and regioselectivity [2]. With our efforts [3–8] to utilize heterocyclic compounds as dipolarophile component in 1,3-dipolar cycloaddition we have chosen 5-acetoxy-2(5*H*)-furanone (**1a**) as a simple model system.

Although its formation [9] and some aspects of its chemistry (**1a** is an effective fungicide [10]) have been investigated in detail, its potential as a reactive dipolarophile has so far been neglected. In this communication [11] we report that it undergoes highly selective cycloaddition reactions with arylnitrile oxides and we compare its behaviour with 5-ethoxy- and 5-hydroxy-2(5*H*)-furanones (**1c**, **1d**). Recently, we have found [12] that 1,3-dipolar cycloaddition of nitrile oxides to **1c** are regio- and stereoselectively affording **3**, whereas the hydroxy compound **1d** affords a 52:48

mixture of both *anti*- and *syn*-diastereoisomers **3** and **4**. The same results were obtained by an asymmetric cycloaddition of benzenenitrile oxide to 5-methyloxy-2(5*H*)-furanone [13].

Results and Discussion

The 5-acetoxy- and 5-benzoyloxy-2(5*H*)-furanones (**1 a**, resp. **1 b**) were prepared by established procedures [9] involving treatment of 5-hydroxy-2(5*H*)-furanone with acetyl and benzoyl chloride. From the reaction of (*X*-substituted) benzenenitrile oxides (**2**) (where *X* is H, 2-Cl, 3-Br, 2,4-diCl, 4-CH_3, 4-OCH_3 and 2,4,6-triCH_3) with **1 a** only one cycloadduct-condensed isoxazoline was isolated. There are four possible adducts of **1 a** and arylnitrile oxide **2**: two regioisomers **3** and **5** resulting from *anti* approach (Fig. 1) of the 1,3-dipole to the acetoxy group (with *exo*-configuration of the acetoxy substituent), and two further isomers **4** and **6** corresponding to *syn* face attack (with *endo*-configuration of the acetoxy substituent). The structure of the isolated adduct as 3-(*X*-phenyl)-4-oxo-6-acetoxy-3 a,4,6,6 a-tetrahydrofuro[3,4-d]isoxazole **3** (for *X* equal H = **3 a**, 2-Cl = **3 b**, 3-Br = **3 c**, 2,4-diCl = **3 d**, 4-CH_3 = **3 e**, 4-OCH_3 = **3 f**, 2,4,6-triCH_3 = **3 g**) was identified from its NMR spectra. ^{13}C-NMR spectroscopy showed that it was a single compound rather than a mixture of isomers and the regio- and stereochemistry was established from its ^{1}H-NMR spectrum (300 MHz). Proton H-6a appears at higher chemical shift (δ 5.43–5.51 ppm) than that for H-3 a (4.81–5.22), establishing that the oxygen atom of the nitrile oxide is attached to the β-carbon of the enone unit of furanone. In contrast, for regioisomers **5** and **6** with the oxygen of the 1,3-dipole linked to the α-carbon the difference between chemical shifts should be greater. A similar mode of addition has been reported earlier for the reaction of arylnitrile oxide with 2(5*H*)-furanone **7** [14] and 5-alkoxy-2(5*H*)-furanone [12, 13] as well as by other enones [15, 16]; it is mainly determined by HOMO, LUMO interactions [17].

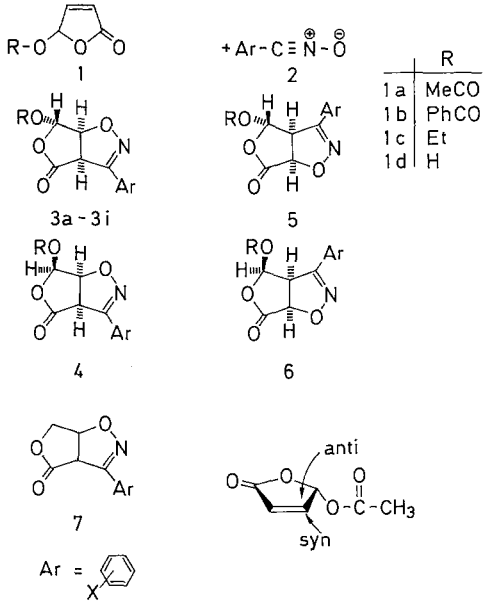

Fig. 1. *Syn* and *anti* cycloadditions to **1 a**

The stereochemistry of the isolated adduct can be deduced from couplings H-3a – H-6a and H-6 – H-6a. The value $J \sim 9$ Hz for the former is characteristic for the *cis*-4,5-dihydroisoxazole unit. The *trans* relationship of the acetal- and H-6a atoms was established by the presence of a singlet which is observed in the ^{1}H-NMR spectrum for the acetal hydrogen atom H-6 in all cases as expected from molecular model studies of the angles between the vicinal hydrogens in a *trans* relationship in these bicyclic products **3** [18] in which the torsion angle H-6 – C-6 – C-6a – H-6a is much greater than that expected for the alternative structure **4**. For the compounds **4** and **6** with the acetoxy group *cis* to the isoxazoline, resulting from *syn* face approach of the 1,3-dipole to the alkene double bond proton H-6a, it should be coupled to both H-3a and H-6 and therefore should appear as a doublet of doublets. The corresponding *syn* adduct from the cycloaddition of **2** with 5-hydroxy-2(5*H*)-furanone exhibits a coupling constants $J_{6-6a} = 4.5$ Hz [12]. A further strong support for structure **3** is provided by the observation that signals of the *o*-aromatic protons are separated from the remaining aromatic signals; this may be explained by a "bent" of the bicyclic system **3**. Neither of the other three possible adducts **4**, **5**, and **6** could be detected despite a careful search. From the reaction of arylnitrile oxides **2** with **1** in addition to **3** only diarylfuroxan and 3,5-diaryl-1,2,4-oxadiazole were isolated.

In order to study the effect of a more bulky substituent at C-5, arylnitrile oxides were reacted with 5-benzoyloxy-2(5*H*)-furanone (**1b**) under similar conditions. The structure of the isolated isoxazolines are the same as those of the corresponding acetoxyderivatives (R = *Ph*CO, for X equal H = **3h**, 4-NO_2 = **3i**).

The cycloadditions to **1a** and **1b** are regio- and stereospecific. The isolated products **3** result from addition to the less hindered face of the furanone with an antiperiplanar relationship between the new C – C bond and the acetoxy or benzoyloxy substituent. Similar selectivity was observed for the corresponding reaction with **1c** [12, 13]. These results also support another investigation [19], which found that cycloadditions of benzenenitrile oxide to *cis*-2,5-dimethoxy-2,5-dihydrofuran proceed stereoselectively *anti*- to the alkoxy substituent, reflecting the energetically favoured diaxial arrangement of the methoxy groups (anomeric effect). Moreover, *syn* orientation of the oxygen-containing substituent relative to the oxygen atom of nitrile oxide leads to greater repulsion in the transition state [9]. The *syn*-cycloaddition took place only in the case of 5-hydroxy-2(5*H*)-furanone, where a hydrogen bond in the transition state can be present [12]. The 1,3-dipolar cycloadditions described here on the lacton moiety are highly regio- and stereoselective. In this way useful precursors for natural product synthesis are accessible.

Experimental Part

Melting points were determined on a Kofler hot plate apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a TESLA BS 487 C (80 MHz) and Varian VXR 300, respectively, and ^{13}C-NMR spectra on JOEL JX-100 and Varian VXR 300 spectrometers, respectively (*TMS* as internal standard, $CDCl_3$, δ-values in ppm, J in Hz), UV spectra on a M-40 (Carl Zeiss Jena) spectrometer in methanol (nm/log ε, ε in $m^2 mol^{-1}$).

Chlorides of benzenehydroximic acids were prepared by chlorination of the corresponding benzaldoximes in chloroform according to [20], the chloride of 4-methoxybenzenehydroximic acid was obtained by treatment of oxime with nitrosyl chloride [21], 2,4,6-trimethylbenzenenitrile oxide was synthesized according to [22]. 5-Acetoxy- and 5-benzoyloxy-2(5*H*)-furanone were prepared by treatment

Table 1. 3-Aryl-4-oxo-6-acetoxy(benzoyloxy)-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazoles **3**

Compound **3**	M.p.[a] (°C)	Yield (%)	Formula[b]	M.w.
a	175.5–177	33	$C_{13}H_{11}NO_5$	261.23
b	127.0–129	41	$C_{13}H_{10}NO_5Cl$	295.67
c	127.5–129	18	$C_{13}H_{10}NO_5Br$	340.13
d	108.0–111	43	$C_{13}H_9NO_5Cl_2$	330.12
e	118.0–121	36	$C_{14}H_{13}NO_5$	275.24
f	138.0–139	55	$C_{14}H_{13}NO_6$	291.24
g	178.0–180	40	$C_{16}H_{17}NO_5$	303.30
h	134.0–138	31	$C_{18}H_{13}NO_5$	323.29
i	199.0–202	27	$C_{18}H_{12}N_2O_7$	368.30

[a] Recrystallized from methanol
[b] Satisfactory microanalysis obtained: C ± 0.30, H ± 0.25, N ± 0.21

of 5-hydroxy-2(5*H*)-furanone with acetyl- and benzoylchloride [9]. 5-Hydroxy-2(5*H*)-furanone was prepared by irradiation in methanol of 2-furancarbaldehyde with a 450 W medium pressure mercury lamp in the presence of Rose-bengal and with introduction of a strong current of air, according to [23].

3-Aryl-4-oxo-6-acetoxy(benzoyloxy)-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazoles **3** (Table 1)

Dry triethylamine (11 mmol) in dry ether (30 ml) was added dropwise at −5–0°C to a stirred cooled solution of the corresponding benzenehydroxime acid chloride (10 mmol) and the dipolarophile (10 mmol) in dry ether (30 ml) during 2 h. After stirring overnight at room temperature, the precipitated triethylammonium chloride was removed by filtration and the filtrate was concentrated in vacuo. The products were triturated with the appropriate solvent or chromatographed on a column of silica gel and purified by crystallization from ethanol or methanol. The cycloaddition of 2,4,6-trimethylbenzenenitrile oxide was performed in the following way: The nitrile oxide (10 mmol) and dipolarophile (10 mmol) in dry benzene (30 ml) were heated to 80°C for 4 h. After cooling, the worked up mixture was concentrated and processed further as described above.

3-Phenyl-4-oxo-6-acetoxy-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazole (**3a**)

UV: 263 (3.17). ^{1}H-NMR: 2.18 (s, 3H, CH_3), 4.83 (d, 1H, H-3a, $J = 9.1$), 5.47 (d, 1H, H-6a, $J = 9.1$), 6.52 (s, 1H, H-6), 7.41–7.49 (m, 3H, aromat. H), 7.87–7.99 (m, 2H, aromat. H). ^{13}C-NMR: 20.76 (q, CH_3), 54.21 (d, C-3a), 86.59 (d, C-6a), 98.28 (d, C-6), 126.34, 127.94, 128.92, 131.19 (aromat. C), 152.24 (s, C-3), 168.59, 168.95 (s, s, C-4, CO).

3-(2-Chlorophenyl)-4-oxo-6-acetoxy-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazole (**3b**)

UV: 248 (2.89). ^{1}H-NMR: 2.18 (s, 3H, CH_3), 5.22 (d, 1H, H-3a, $J = 9.3$), 5.50 (d, 1H, H-6a, $J = 9.3$), 6.54 (s, 1H, H-6), 7.31–7.56 (m, 4H, aromat. H). ^{13}C-NMR: 20.68 (q, CH_3), 55.25 (d, C-3a), 86.34 (s, C-6a), 98.27 (d, C-6), 125.26, 127.28, 130.60, 131.72, 131.96, 133.05 (aromat. C), 152.01 (d, C-3), 168.52 (s, s, C-4 and CO).

3-(3-Bromophenyl)-4-oxo-6-acetoxy-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazole (**3c**)

UV: 265 (3.15). ^{1}H-NMR: 2.19 (s, 3H, CH_3), 4.81 (d, 1H, H-3a, $J = 9.3$), 5.51 (d, 1H, H-6a, $J = 9.3$), 6.52 (s, 1H, H-6), 7.26–8.11 (m, 4H, aromat. H). ^{13}C-NMR: 20.75 (q, CH_3), 54.00 (d, C-3a), 86.94 (d, C-6a), 98.29 (d, C-6), 122.98, 126.57, 128.34, 130.42, 130.62, 134.10 (aromat. C), 151.19 (s, C-3), 168.61, 168.73 (s, s, C-4, CO).

3-(2,4-Dichlorophenyl)-4-oxo-6-acetoxy-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazole (**3d**)

UV: 256 (2.95). ^{1}H-NMR: 2.18 (s, 3H, CH_3), 5.19 (d, 1H, H-3a, $J = 9.0$), 5.50 (d, 1H, H-6a, $J = 9.0$), 6.53 (s, 1H, H-6), 7.32–7.54 (m, 3H, aromat. H). ^{13}C-NMR: 20.71 (q, CH_3), 55.05 (d, C-3a), 86.51 (d, C-6a), 98.29 (d, C-6), 123.84, 127.77, 130.64, 132.49, 133.86, 137.63 (aromat. C), 151.22 (s, C-3), 168.42, 168.50 (s, s, C-4, CO).

3-(4-Methylphenyl)-4-oxo-6-acetoxy-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazole (**3e**)

UV: 268 (3.17). ^{1}H-NMR: 2.18 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.82 (d, 1H, H-3a, $J = 9.0$), 5.45 (d, 1H, H-6a, $J = 9.0$), 6.52 (s, 1H, H-6), 7.25 (d, 2H, aromat. H), 7.81 (d, 2H, aromat. H). ^{13}C-NMR: 20.75 (q, CH_3), 21.54 (q, CH_3), 54.28 (d, C-3a), 86.41 (d, C-6a), 98.26 (d, C-6), 123.49, 127.69, 129.64, 141.69 (aromat. C), 152.23 (s, C-3), 168.61, 169.08 (s, s, C-4, CO).

3-(4-Methoxyphenyl)-4-oxo-6-acetoxy-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazole (**3f**)

UV: 279 (3.22). ^{1}H-NMR: 2.18 (s, 3H, CH_3), 3.85 (s, 3H, CH_3O), 4.81 (d, 1H, H-3a, $J = 9.0$), 5.43 (d, 1H, H-6a, $J = 9.0$), 6.51 (s, 1H, H-6), 6.94–6.97 (m, 2H, aromat. H), 7.85–7.88 (m, 2H, aromat. H). ^{13}C-NMR: 20.75 (q, CH_3), 54.43 (d, C-3a), 55.41 (q, CH_3O), 86.28 (d, C-6a), 98.32 (d, C-6), 114.37, 118.76, 129.63, 161.85 (aromat. C), 151.78 (s, C-3), 168.61, 169.21 (s, s, C-4, CO).

3-(2,4,6-Trimethylphenyl)-4-oxo-6-acetoxy-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazole (**3g**)

^{1}H-NMR: 2.19 (s, 3H, CH_3), 2.20 (s, 6H, CH_3), 2.30 (s, 3H, CH_3CO), 4.59 (d, 1H, H-3a, $J = 9.1$), 5.48 (d, 1H, H-6a, $J = 9.1$), 6.55 (s, 1H, H-6), 6.92 (s, 2H, aromat. H). ^{13}C-NMR: 19.74 (q, diCH_3), 20.72 (q, CH_3), 21.17 (q, CH_3), 57.42 (d, C-3a), 85.28 (d, C-6a), 99.07 (d, C-6a), 121.97, 128.91, 136.96, 139.98 (aromat. C), 152.37 (s, C-3), 168.42, 168.59 (s, s, C-4, CO).

3-Phenyl-4-oxo-6-benzoyloxy-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazole (**3h**)

UV: 233 (3.27), 263 (3.20). ^{1}H-NMR: 4.98 (d, 1H, H-3a, $J = 9.3$), 5.66 (d, 1H, H-6a, $J = 9.3$), 6.71 (s, 1H, H-6), 7.44–7.67 (m, 6H, aromat. H), 7.94–8.07 (m, 4H, aromat. H). ^{13}C-NMR: 54.54 (d, C-3a), 86.87 (d, C-6a), 99.37 (d, C-6), 126.40, 127.97, 128.76, 128.93, 130.13, 131.18, 134.42 (aromat. C), 152.30 (s, C-3), 164.46 (s, CO), 169.08 (s, C-4).

3-(4-Nitrophenyl)-4-oxo-6-benzoyloxy-3a,4,6,6a-tetrahydrofuro[3,4-d]-isoxazole (**3i**)

UV: 229 (3.21), 299 (3.19). ^{1}H-NMR (in *DMSO-d_6*): 5.77 (d, 1H, $J = 9.0$, H-3a), 5.97 (d, 1H, $J = 9.0$, H-6a), 6.87 (s, 1H, H-6), 7.58–8.09 (m, 5H, aromat. H), 8.16 (d, 2H, $J = 8.7$, aromat. H), 8.38 (d, 2H, $J = 8.7$, aromat. H). ^{13}C-NMR (in *DMSO-d_6*): 53.12 (d, C-3a), 87.47 (d, C-6a), 98.45 (d, C-6), 124.06, 127.90, 129.02, 129.83, 132.58, 134.56, 148.57 (aromat. C), 152.08 (s, C-3), 163.87 (s, CO), 170.04 (s, C-4).

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