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1,3-Dipolar Cycloadditions To 5-Methoxy-2(5*H*)-Furanone

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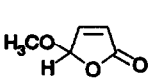
Abstract: Various nitrile oxides and nitrones, ethyl diazoacetate and an azomethine ylide were examined in 1,3-dipolar cycloadditions to 5-methoxy-2[5H]-furanone, in particular with respect to regio- and diastereoselectivities. Isoxazoles **13-17** and isoxazolidines **21**, **22** and **24** were obtained in high yields with *anti*-facial selectivities and regioselectivities exceeding 95%. In the case of pyrazoline **26** minor amounts of *syn*-facial adduct are also observed, whereas lactone annulated pyrrolidines **28** are obtained as mixtures of regio-isomers.

Introduction

The 1,3-dipolar cycloaddition reactions of nitrones and nitrile oxides to alkenes have been extensively used for the preparation of isoxazolidines and isoxazoles.[1,2] Further transformations offer access to a variety of functional intermediates for synthesis, in many cases with multiple stereogenic centers introduced during the cycloaddition proces. Cycloadditions to α,β-unsaturated carboxylic acid derivatives are particularly useful due to high regioselectivity often observed,[3,4,5] as is illustrated by various Diels-Alder and 1,3-dipolar cycloadditions to butenolides.[6]



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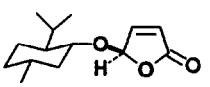
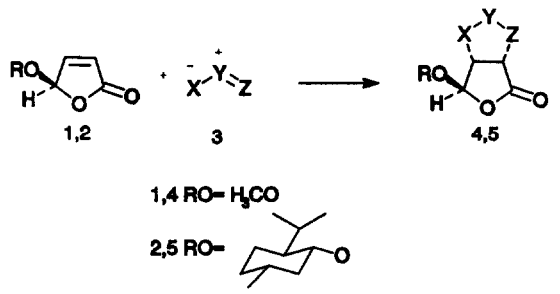


2

Figure 1

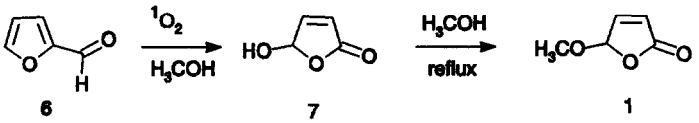
Fariña *et al.* reported the regioselective diazomethane addition to racemic 5-methoxy-2(5H)-furanone (**1**), however poor diastereoselectivity was obtained.[7] We have shown that high levels of stereoselectivity can be reached in asymmetric cycloadditions to 5(*l*)-menthyloxy-2(5H)-furanone (**2**).[6,8] The prospect of preparing optically active multifunctional compounds by 1,3-dipolar cycloadditions to γ-alkoxybutenolides with high stereocontrol is very attractive (Scheme 1).



Scheme 1

Recently a number of stereochemical studies on the 1,3-dipolar cycloadditions of nitrones to 2(5H)-furanones have been reported.[6,9] It has been shown that the endo-mode of addition to these butenolides is not the major route for cyclic nitrones. In some of these cases appreciable levels of diastereoselectivity can be reached.[10] As part of our program to investigate the scope and stereoselectivity of cycloaddition reactions to γ-alkoxybutenolides[11,12] nitrone and nitrile oxide additions to 5-methoxy-2(5H)-furanone (**1**) were conducted. Furthermore the diazoacetic ester addition and an azomethine ylide addition to **1** are described. Important aspects are the assignment of the stereochemistry of the cycloadducts and the elucidation of the stereoselectivity in 1,3-dipolar cycloadditions to γ-alkoxybutenolides.

The starting material 5-methoxy-2(5H)-furanone (**1**) is readily prepared via Rose Bengal sensitized photooxidation of furfural (**6**) in methanol to 5-hydroxy-2(5H)-furanone (**7**) followed by acetal formation with methanol (Scheme 2).[13]

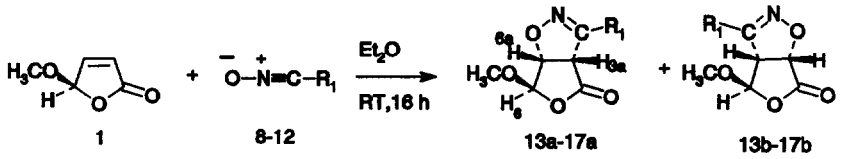


Scheme 2

Nitrile oxide additions

The nitrile oxides **8-12** were prepared *in situ* by dehydrohalogenation of the corresponding hydroximic acid chloride using triethylamine as a base.[14] The reactions of methoxybutenolide **1** with these nitrile oxides were performed at room temperature in diethylether (Scheme 3).

Besides benzonitrile oxide, arylnitrile oxides with electron donor and acceptor substituents, an α,β-unsaturated nitrile oxide and an aliphatic nitrile oxide were studied. The results of these 1,3-dipolar cycloadditions are summarized in **Table 1.**



Scheme 3

Table 1. Addition of Nitrile Oxides 8-12 to 5-Methoxy-2(5H)-Furanone (1)

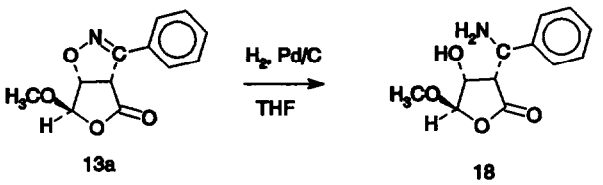
Entry	Nitrile oxide	R_1	Products	Yield (%)[a]
1	8	C_6H_5	13a,b	71
2	9	p-ClC_6H_4	14a,b	68
3	10	p-$MeOC_6H_4$	15a,b	65
4	11	$CH{=}CHC_6H_5$	16a,b	62
5	12	$CH(CH_3)_2$	17a,b	65

[a] Chemical yields of isolated pure adducts **13a - 17a**.

The reaction of each nitrile oxide **8-12** afforded one major cycloadduct **13a-17a** in good yield, whereas only minor amounts (< 10%) of the regioisomeric cycloadduct **13b-17b** were found. The regiochemistry is deduced from ^{1}H NMR data and NOESY experiments. The ^{1}H NMR absorptions for H_{3a} in **13a-17a** are shifted downfield compared to the absorptions for **13b-17b** (e.g. δ 4.72 ppm for **13a** and 4.43 ppm for **13b** respectively) and furthermore a NOE enhancement is seen between H_{3a} and the *ortho*-aryl hydrogens in **13a-17a**. The observed regiochemistry in the main product is remarkable considering the low regioselectivity generally observed in nitrile oxide additions.[15] Poor regioselectivity has been reported in cycloadditions to crotonoyl derivatives,[17] whereas reverse regioselectivity is found in nitrile oxide additions to acrylic acid derivatives.[16] However, excellent diastereofacial selectivity is observed in all nitrile oxide additions described here. The acetal proton H_6 appears as a singlet which implies a trans relationship between H_{6a} and H_6 and an *anti*-facial approach of the nitrile oxide with respect to the methoxy-substituent. This analysis is confirmed by molecular modelling studies and is in accordance with the complete π-face selective Diels-Alder reactions, amine and thiol additions and tandem 1,4-addition-alkylations to **1**[8,12] and the preferred anti-selectivity in nitrone additions to 5-alkylbutenolides.[10] (*vide infra*)

It should be noted that yields and stereoselectivities hardly depend upon the nature of the nitrile oxide. Furthermore, enantiomerically pure isoxazoles are obtained in similar nitrile oxide additions to 5-(*l*)-menthyloxy-2(5H)-furanone (**2**).[6]

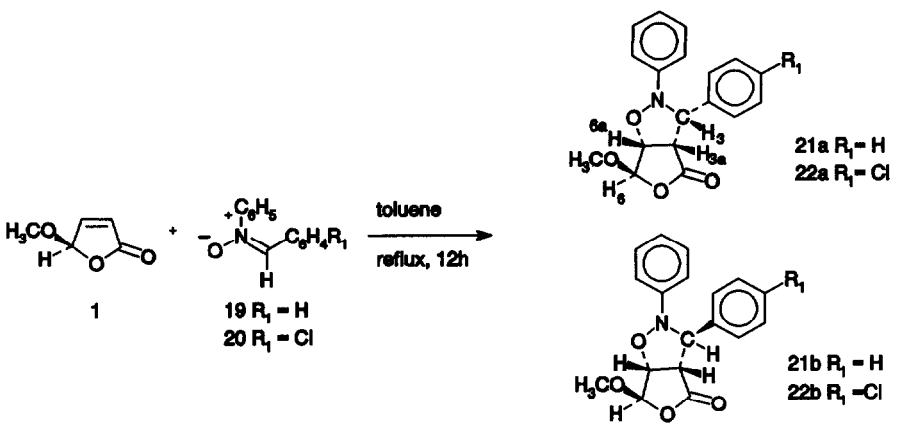
Reductive isoxazole ring opening can readily be achieved (Scheme 4). Thus N-O bond cleavage and stereoselective imine reduction provides multifunctional lactone **18** as a single isomer.



Scheme 4

Nitrone additions

The diarylnitrones **19** and **20** were prepared using literature procedures.[18] The reaction between 5-methoxy-2(5H)-furanone (**1**) and nitrones **19** and **20** was performed in toluene at reflux (Scheme 5). The cycloadditions afforded in each case two diastereoisomeric isoxazolidines, **21a** and **21b** (ratio 65 : 35) or **22a** and **22b** (ratio 68 : 32) respectively.

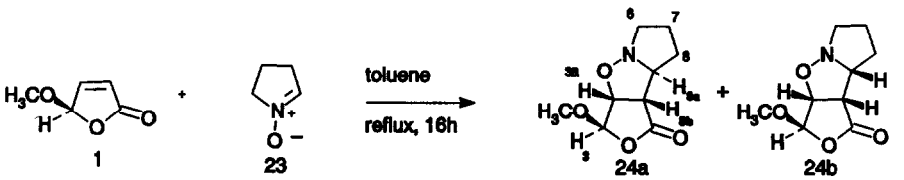


Scheme 5

NMR chemical shifts and coupling patterns of the H_{3a} and H_{6a} protons support the regiochemistry as indicated for all four compounds. In particular the upfield H_{3a} proton relative to the downfield H_{6a} absorption (**22a**, H_{3a}: δ = 3.8, H_{6a}: δ = 4.9, **22b**, H_{3a}: δ = 3.6, H_{6a}: δ = 5.0 ppm) excludes the alternative isoxazolidine structure.[9,10] The regioselectivity is not unexpected as many examples have been reported of nitrone additions to electron deficient alkenes affording isoxazolidines with the oxygen β to the electron-withdrawing group.[6,10,19] In isoxazolidines **21** and **22** the acetal hydrogen (H_6) appears either as a singlet or a doublet with a small coupling constant (i.e. for **22b** J_{H6H6a} = 1.25 Hz), which implies a *trans*-relationship between H_6 and H_{6a}. This means that *face*-selective addition of nitrones **19** and **20** has taken place anti to the γ-methoxy substituent. The complete *face*-selective cycloaddition again demonstrates the powerful directing effect of the γ-

alkoxy-substituent as observed before in nitrile oxide (vide infra) and Diels-Alder type[11] cycloadditions to **1**. The isomeric cyclo-adducts **21a** and **21b** (as well as **22a** and **22b**) were separated by column chromatography and obtained in analytically pure form. The *endo* stereochemistry is assigned to the major isomers **21a** and **22a** based on extensive NMR (COSY, NOESY) investigations. Most relevant is the smaller value of the coupling constant $J_{H3a,H3}$ for the *exo*-isomer (**22a** $J_{H3a,H3}$= 8.5 Hz, **22b** $J_{H3a,H3}$ = 2.4 Hz) and the presence of NOE interactions between H_{3a} and the *ortho*-aryl hydrogens in the *exo*-isomer **21b** (**22b**) which NOE effects are absent in the NOESY spectra of **21a** (**22a**). The observation of *endo*-selectivity in these nitrone additions is not unexpected considering the preferred endo-addition of acyclic nitrones to maleimide, dimethyl maleate and maleic anhydride.[10,20] The endo-control is presumably determined by stabilizing secondary orbital interactions.[10]

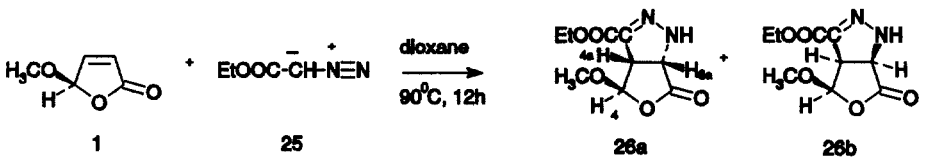
The 1,3-dipolar cycloaddition between 3,4-dihydro-2H-pyrrole-1-oxide (**23**)[9,21] and **1** was performed in toluene at reflux. Cycloadducts **24a** and **24b** were obtained in a 7 : 1 ratio in 91% yield. NMR analysis, as described above, showed that no regioisomers are formed and that *anti*-facial addition again has occurred. The major diastereoisomer **24a** was isolated by column chromatography (75% yield) and the relative configuration of **24a** and **24b** was established via the magnitude of $J_{H8a,H8b}$. For **24a**, J = 0 Hz indicates a trans relationship between H_{8a} and H_{8b}, which implies that the main product has the *exo* stereochemistry (Scheme 6).



Scheme 6

Diazoacetic ester addition

The addition of ethyl diazoacetate to 5-methoxy-2(5H)-furanone (**1**) at 90 °C in dioxane resulted in two pyrazolines **26a** and **26b** (ratio 91 : 9) in 65% yield (Scheme 7). The major isomer is formed by the *anti*-facial approach, as is evident from the singlet observed for the acetal hydrogen (H_4). In contrast $J_{H4a,H4}$ = 7.0 Hz for the minor isomer is in accordance with a *syn* orientation of the pyrazoline ring and methoxy-substituent. The formation of (minor amounts of) *syn*-facial adduct **26b** is remarkable regarding the commonly observed complete *anti*-facial additions of various 1,3-dipoles and dienes to γ-alkoxybutenolides.[11,12] It should be noted that isomerization to the 2-pyrazoline structure has occurred and therefore no 1-pyrazoline isomers were found.

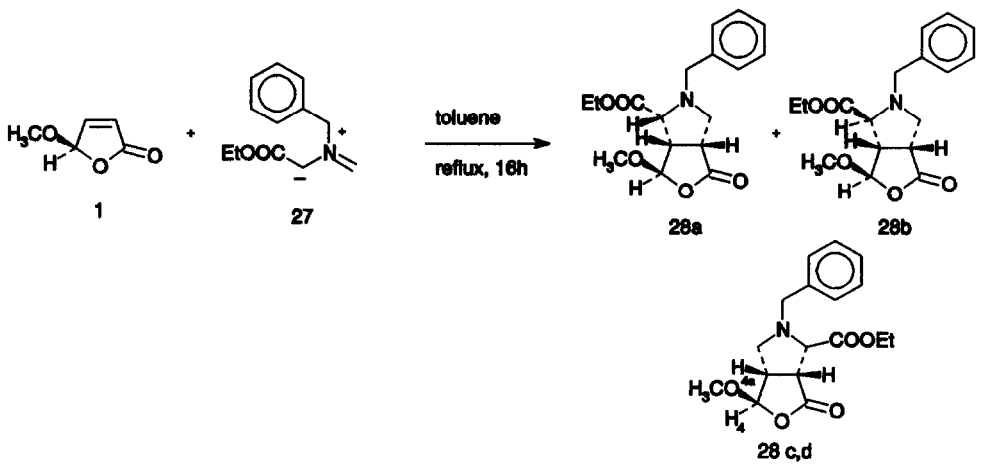


1 25 26a 26b

Scheme 7

Azomethine ylide addition

Azomethine ylides represent a frequently used class of 1,3-dipolar reagents giving access to a variety of substituted pyrrolidines.[22] The ester-substituted azomethine ylide **27** was prepared *in situ*



1 27 28a 28b 28 c,d

Scheme 8

from *N*-benzylglycine and formaldehyde[23]. Heating butenolide **1** with **27** in toluene afforded cycloadducts **28a-28d** in a 3 : 3 : 4 ratio (Scheme 8). The isomers **28a** and **28b** were separated by column chromatography whereas the epimers **28c** and **28d** were obtained as a mixture. The stereochemical assignment is based on complete analysis by NMR techniques. Although the regio selectivity (3 : 2 ratio) in the 1,3-dipolar cycloaddition with **27** is poor, complete *anti*-π-facial selectivity is observed again. Small coupling constants ($J_{H4,H4a}$ < 2 Hz) indicate a trans relationship between the methoxy substituent and the pyrrolidine ring. Both *endo*- and *exo*-adducts (**28a** and **28b**) of the regioisomers, as depicted, are found in the reaction of ylide **27**. From the results it is clear that, despite the easy formation of multifunctional pyrrolidines via this cycloaddition process, the low selectivity limits its use in further synthetic applications. These problems, however, might be eliminated with the use of *N*-(trimethylsilylmethyl)aminomethyl ethers as azomethine ylide synthons under less severe conditions.[24]

It can be concluded that multifunctional (lactone annulated) isoxazolines and isoxazolidines, pyrazolines and pyrrolidines are accessible via 1,3-dipolar additions to γ-methoxybutenolide **1**. In several cases high regio- and diastereoselectivities are observed which make these reactions particularly valuable in heterocyclic and natural product synthesis. Furthermore these results will be useful in routes to optically active analogues of the cycloadducts described here, based on similar additions to γ-menthyloxybutenolide **2**.

EXPERIMENTAL SECTION

Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. ^{1}H NMR spectra were recorded on a Varian Gemini-200 spectrometer (at 200 MHz), or a Varian VXR-300 spectrometer (at 300 MHz) where indicated, using $CDCl_3$ as a solvent. Chemical shifts are denoted in δ units (ppm) relative to tetramethylsilane (TMS) as an internal standard at δ = 0.00 ppm. ^{13}C NMR spectra were recorded on a Varian Gemini-200 spectrometer (at 50.3 MHz), or a Varian VXR-300 spectrometer (at 76.9 MHz) where indicated, using $CDCl_3$ as solvent. The chemical shifts are denoted in δ units (ppm) with the solvent as an internal standard and converted to the TMS scale using δ ($CDCl_3$) = 76.91 ppm. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), ddd (double double doublet), t (triplet), dt (double triplet), q (quartet), se (septet), m (multiplet) and br (broad). High Resolution Mass Spectra (HRMS) were obtained on a AEI MS-902 spectrometer by Mr A. Kiewiet. All commercially available chemicals were obtained from Janssen Chimica or Aldrich and were used without further purification, except silica gel 60 mesh which was obtained from Merck.

General procedure for the 1,3-dipolar cycloaddition of nitrile oxides 8 - 12 to 5-methoxy-2(5*H*)-furanone 1

6-Methoxy-3-phenyl-3a,4,6,6a-tetrahydro-furo[3,4-d]isoxazol-4-one (13a)

To a stirred solution of 5-methoxy-2(5H)-furanone **1** (1.00 g, 8.77 mmol) and benzaldehyde chloroxime (2.04 g, 13.2 mmol, 1.5 equiv.) in Et_2O (50 mL) was added very slowly triethylamine (2.65 g, 26.3 mmol, 3 eq.) dissolved in ether (50 mL). After stirring for 16 h at room temperature H_2O (100 mL) was added, the Et_2O layer was separated and the H_2O layer was extracted with Et_2O (1 x 50 mL). The combined organic layers were dried ($NaSO_4$) and evaporated to afford a brown oil. The products **13a** and **13b** were separated by column chromatography (silica gel, CH_2Cl_2). Crystallization from methanol afforded pure **13a** as a white solid (1.46 g, 6.3 mmol, 71%), mp 119.6-120.4 °C: ^{1}H NMR: δ = 3.60 (s, 3H, OCH_3), 4.72 (d, J = 9.0 Hz, 1H, CCHC, (H-3a)), 5.28 (d, J = 9.0 Hz, 1H, CCHO, (H-6a)), 5.56 (s, OCHO, (H-6)), 7.44 (m, 3H, Ar, CH=CH), 7.94 (m, 2H, Ar, CH=CH); ^{13}C NMR: δ =

53.94 (q), 57.48 (d), 86.93 (d), 107.90 (d), 126.66 (s, Ar), 127.90(d, Ar), 128.83 (d, Ar), 130.98 (d, Ar), 152.58 (s, C=N), 169.74 (s, C=O); HRMS calcd for $C_{12}H_{11}NO_4$: 233.069. Found 233.069; Anal. calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.42; H, 4.80; N, 5.90.

3-(4-Chlorophenyl)-6-methoxy-3a,4,6,6a-tetrahydro-furo[3,4-d]isoxazol-4-one (14a)

Starting from 5-methoxy-2(5H)-furanone **1** (0.60 g, 5.26 mmol) and p-chlorobenzaldehyde chloroxime[14] (1.50 g, 7.90 mmol, 1.5 eq.), provided **14** (ratio **14a** : **14b** = 91 : 9) and subsequent crystallization from methanol yielded **14a** as a white solid (0.96 g, 3.59 mmol, 68 %), mp 153.7-156.6 °C: ^{1}H NMR: δ = 3.61 (s, 3H, OCH_3), 4.68 (d, J = 9.3 Hz, 1H, CCHC, (H-3a)), 5.29 (d, J = 9.4 Hz, 1H, CCHO, H-6a), 5.57 (s, 1H, H-6), 7.42 (m, 2H, Ar, CH=CH), 7.88 (m, 2H, Ar, CH=CH); ^{13}C NMR: δ = 53.70 (q), 57.36 (d), 86.97 (d), 107.8 (d), 125.03 (s, Ar), 129.00 (d, Ar), 136.93 (s, Ar), 151.55 (s, C=N), 169.46 (s, C=O); HRMS calcd for $C_{12}H_{10}NO_4Cl$: 267.030 Found 267.030; Anal. calcd for $C_{12}H_{10}NO_4Cl$: C, 53.85; H, 3.77; N, 5.23; Cl, 13.25. Found: C, 53.68; H, 3.77; N, 5.38; Cl, 13.12.

3-(4-Methoxyphenyl)-6-methoxy-3a,4,6,6a-tetrahydro-furo[3,4-d]isoxazol-4-one (15a)

Following the general procedure described for **13**, 5-methoxy-2(5H)-furanone **1** (0.80 g, 7.02 mmol) and p-methoxybenzaldehyde chloroxime[14] (2.31 g, 7.1 mmol, 1.8 eq.) afforded **15** (ratio **15a** : **15b** = 9 : 1). After crystallization from methanol **15a** was obtained as a white solid (1.14 g, 4.6 mmol, 65 %), mp 136.5-138.2 °C: ^{1}H NMR: δ = 3.60 (s, 3H, OCH_3), 3.86 (s, 3H, Ar-OCH_3), 4.68 (d, J = 9.2 Hz, 1H, CCHC, (H-3a)), 5.24 (d, J = 9.2 Hz, 1H, CCHO, (H-6a)), 5.56 (s, 1H, H-6), 6.95 (d, 2H, Ar, CH=CH), 7.88 (d, 2H, Ar, CH=CH); ^{13}C NMR; δ = 54.21 (q), 55.37 (q), 57.47 (d), 66.61 (d), 107.93 (d), 114.28 (d, Ar), 119.10 (d, Ar), 129.60 (s, Ar), 152.06 (s, C=N), 161.72 (s, Ar), 169.89 (s, C=O); HRMS calcd for $C_{13}H_{13}NO_5$: 263.079. Found 263.079; Anal. calcd for $C_{13}H_{13}NO_5$: C, 59.31; N, 5.32; H, 4.98. Found: C, 59.25; N, 5.53; H, 4.91.

6-Methoxy-3-(2-styryl)-3a,4,6,6a-tetrahydro-furo[3,4-d]isoxazol-4-one (16a)

Starting from 5-methoxy-2(5H)-furanone **1** (0.13 g, 1.14 mmol) and cinnamaldehyde chloroxime[14] (0.31 g, 1.7 mmol, 1.5 eq.) **16** was obtained (ratio **16a** : **16b** = 95.5 : 4.5) and subsequent column chromatography (silica gel, CH_2Cl_2) afforded **16a** as yellowish crystals (0.18 g, 0.70 mmol, 61 %), mp 162.3-163.6 °C: ^{1}H NMR: δ = 3.59 (s, 3H, OCH_3), 4.58 (d, J = 9.4 Hz, 1H, CCHC, (H-3a)), 5.27 (d, J = 9.0 Hz, 1H, CCHO, (H-6a)), 5.52 (s, 1H, H-6), 6.95 (d, J = 11.4 Hz, CH=C), 7.24-7.55 (m, 6H, Ar, CH=CH, CH=C); ^{13}C NMR: δ = 53.41 (q), 57.53 (d), 86.86 (d), 108.06 (d), 114.33 (d,C=C), 127.37 (d, Ar), 128.86 (d, Ar), 129.51 (d, Ar), 135.41 (s, Ar), 140.41 (d, C=C), 153.21 (s, C=N), 169.69 (s, C=O). HRMS calcd for $C_{14}H_{13}NO_4$: 259.084. Found 259.084; Anal. calcd for $C_{14}H_{13}NO_4$: C, 64.86; N, 5.40; H, 5.05. Found: C, 65.21; N, 5.71; H, 4.99.

6-Methoxy-3-(1-methylethyl)-3a,4,6,6a-tetrahydro-furo[3,4-d]isoxazol-4-one (17a)

Starting from 5-methoxy-2(5H)-furanone **1** (0.8 g, 7.0 mmol) and isobutyraldehyde chloroxime[14] (1.27 g, 10 mmol, 1.4 eq.), **17a** was obtained as white crystals after crystallization from methanol (0.90 g, 45 mmol, 65 %), mp 78.0-78.1 °C: ^{1}H NMR δ = 1.25 (d, J = 6.8 Hz, 3H, CH_3 *i*-butyl), 1.27 (d, J = 6.8 Hz, 3H, CH_3 *i*-butyl), 2.86 (se, J = 6.8 Hz, 1H, CH *i*-butyl), 3.54 (s, 3H, OCH_3), 4.29 (d, J = 9.3 Hz, 1H, CCHC, H-3a), 5.05 (d, J = 9.3 Hz, 1H, CCHO, H-6a), 5.42 (s, 1H, H-6); ^{13}C NMR: δ = 19.07 (q), 20.39 (q), 26.47 (d), 55.16 (q), 57.44 (d), 85.43 (d), 108.94 (d), 158.61 (s, C=N), 169.94 (s, C=O). HRMS calcd for $C_9H_{13}NO_4$: 199.084. Found 199.084; Anal. calcd for $C_9H_{13}NO_4$: C, 54.26; N, 7.03; H, 6.58. Found: C, 54.73; N, 7.08; H, 6.47.

2,3-Diphenyl-6-methoxy-3,3a,6,6a-tetrahydro-4H-furo[3,4-d]isoxazol-4-one (21a,b)

To N-phenyl-phenylnitrone **19**[18] (1.95 g, 9.70 mmol, 1.1 eq.) dissolved in toluene (20 mL) was added a solution of 5-methoxy-2(5H)-furanone **1** (1.00 g, 8.86 mmol) in toluene (30 mL). The clear solution was refluxed for 12 h, cooled to room temperature and after evaporation of the solvent a brown oil was obtained. Compounds **21a** and **21b** were separated by column chromatography (silica gel, CH_2Cl_2 : hexane, 1 : 3) as white solids (**21a** 1.50 g, 4.82 mmol, 54%; **21b** 0.32 g, 1.02 mmol, 12%), **21a:** mp = 110.1-110.7 °C: ^{1}H NMR: δ = 3.60 (s, 3H, OCH_3), 3.90 (dd, J_1 = 6.4 Hz, J_2 = 8.6 Hz, 1H, CCHC, (H-3a)), 4.80 (d, J = 8.6 Hz, 1H, NCHC, (H-3)), 4.90 (d, J = 6.4 Hz, 1H, CCHO, (H-6a)), 5.62 (s, 1H, OCHO, (H-6)), 7.06-7.42 (m, 10H, Ar, CH=CH); **21b** ^{1}H NMR: δ = 3.57 (s, 3H, OCH_3), 3.65 (dd, J_1 = 2.4 Hz, J_2 = 6.4 Hz, 1H, CCHC, (H-3a)), 4.83 (d, J = 6.4 Hz, 1H, CCHO, (H-6a)), 4.97 (d, J = 2.4 Hz, 1H, NCHC, (H-3)), 5.54 (s, 1H, OCHO, (H-6)), 6.84-7.40 (m, 10H, Ar, CH=CH); **21a** ^{13}C NMR δ = 55.22 (q), 57.47 (d), 72.14 (d), 82.34 (d), 107.98 (d), 118.49 (d), 124.58 (d), 127.71 (d), 128.69 (d), 128.83 (d), 134.59 (s), 147.81 (s), 171.93 (s); HRMS calcd for $C_{18}H_{17}NO_4$: 311.116. Found 311.116; Anal. calcd for $C_{18}H_{17}NO_4$: C, 69.44; N, 4.50; H, 5.49. Found C, 69.28 N, 4.50; H, 5.42.

3-(4-Chlorophenyl)-6-methoxy-2-phenyl-3,3a,6,6a-tetrahydro-4H-furo[3,4-d]isoxazol-4-one (22a,b)

These compounds were prepared in an identical way as described for **21a** and **21b**. Starting from N-phenyl-p-chlorophenylnitrone **20**[18] (3.1 g, 13.4 mmol) and 5-methoxy-2(5H)-furanone **1** (1.5 g, 13.4 mmol), the compounds **22a** and **22b** were obtained as oils (cis : trans ratio = 68 : 32, estimated by ^{1}H NMR analysis). Compounds **22a** and **22b** were separated by column chromatography (silica gel, CH_2Cl_2 : hexane, 3 : 1) as white solids (**22a** 1.71 g, 4.95 mmol, 54%; **22b** 0.38 g, 1.10 mmol, 12%), **22a**: mp 102.1-102.3 °C: ^{1}H NMR: δ = 3.6 (s, 3H, OCH_3), 3.8 (dd, J_1 = 8.8 Hz, J_2 = 7.7 Hz, 1H, CCHC, (H-3a)), 4.8 (d, J = 8.8 Hz, 1H, NCHC, (H-3)), 4.9 (dd, J_1 = 1.3 Hz, J_2 = 7.7 Hz, 1H, OCHC, (H-6a)), 5.6 (d, J = 1.3 Hz, 1H, OCHO, (H-6)), 6.9-7.4 (m, 9H, Ar, CH=CH); **22b** ^{1}H NMR: δ = 3.55 (s, 3H, OCH_3), 3.65 (dd, J_1 = 2.3 Hz, J_2 = 6.5 Hz, 1H, CCHC, (H-3a)), 4.8 (d, J = 6.5 Hz,

1H, OCHC, (H-6a)), 5.0 (d, J = 2.3 Hz, 1H, NCHC, (H-3)), 5.6 (s, 1H, OCHO, (H-6)), 6.9-7.4 (m, 9H, Ar, CH=CH); **22a:** ^{13}C NMR: δ = 55.0 (q), 57.5 (d), 71.4 (d), 82.4 (d), 107.8 (d), 118.6 (d), 124.9 (d), 128.9 (d), 129.0 (d), 129.1 (d), 133.3 (s), 134.4 (s), 147.6 (s, C=N), 172.0 (s, C=O); HRMS calcd for $C_{18}H_{16}NO_4Cl$: 345.077. Found 345.077; Anal. calcd for $C_{18}H_{16}NO_4Cl$: C, 62.52; N, 4.05 H, 4.66; Cl, 10.25. Found: C, 62.53; N, 4.11; H, 4.71; Cl, 10.20.

3-Methoxy-1,3,3a,6,7,8,8a,8b-octahydro-furo[3,4-d]pyrrolo[1,2-b]isoxazol-1-one (24a)

A solution of 3,4-dihydro-2H-pyrrole-1-oxide **23**[9,21] (0.80 g, 9.4 mmol) and 5-methoxy-2(5H)-furanone **1** (1.07 g, 9.4 mmol) in toluene (70 mL) was heated under reflux for 16 h. After evaporation of the solvent the resulting brown oil was filtered over silica gel with ethyl acetate/MeOH (49:1). After evaporation of the solvents a colorless oil was obtained, which proved to be a mixture of **24a** and **24b** (1.70 g, 8.6 mmol, 91 %). ^{1}H NMR indicated a cis/trans ratio of 7 : 1 The products were separated by column chromatography (silica gel, hexane : ethylacetate, 1 : 1). Because of tailing problems only the major product was isolated. After distillation the product was obtained pure as an oil (1.4 g, 7.04 mmol, 75 %), ^{1}H NMR: δ = 1.50-2.20 (m, 4H, CH_2CH_2 (H-7, H-8)), 2.80-3.20 (dt, J_1 = 13,9 Hz, J_2 =8.1 Hz, 1H, NCHH, (H-6)), 3.24-3.37 (ddd, J_1 = 13.9 Hz, J_2 = 7.5 Hz, J_3 = 3.6 Hz, 1H, NCHH, (H-6)), 3.43 (d, J = 6.9 Hz, 1H, CCHC, (H-8b)), 3.52 (s, 3H, OCH_3), 3.83 (t, J = 7.8 Hz, 1H, CCHC, (H-8a)), 4.55 (d, J = 6.9 Hz, 1H, CCHO, (H-3a)), 5.34 (s, 1H, OCHC, (H-3)); ^{13}C NMR: δ = 24.05 (t), 29.66 (t), 53.94 (d), 56.17 (t), 56.87 (d), 70.22 (d), 80.53 (d), 108.19 (d), 175.49 (s, C=O); HRMS calcd for $C_9H_{13}NO_4$: 199.084. Found 199.084; Anal. calcd for $C_9H_{13}NO_4$: C, 54.26; N, 7.03; H, 6.58. Found: C, 53.78; N, 6.84; H, 6.57.

3-Carbethoxy-4-methoxy-1,3a,4,6a-tetrahydro-6H-furo[3,4-c]pyrazol-6-one (26a,b)

A solution of 5-methoxy-2(5H)-furanone **1** (1.00 g, 8.8 mmol) and ethyldiazoacetate **25** (1.15 g, 10.1 mmol) in dioxane (10 mL) was stirred and heated at 90-100 °C for 12 h. After evaporation of the solvent a semi-solid was obtained. ^{1}H NMR analysis showed the presence of **26a** and **26b** in a 91:9 ratio. Crystallization of this residue from ether : hexane (1 : 1,5 mL) afforded a yellow solid (1.30 g, 5.7 mmol, 64.8 %, ratio **26a:26b** = 91:9), mp 129.1-130.2 °C: ^{1}H NMR: δ = 1.32 (t, J = 7.0 Hz, 3H, CH_3CH_2, **26a** and **26b**), 3.50 (s, 0.27H, OCH_3, **26b**), 3.58 (s, 2.73H, OCH_3, **26a**), 4.02 (d, J = 10.0 Hz, 1H, CCHC (H-3a), **26a** and **26b**), 4.32 (q, J = 7.0 Hz, 2H, CH_2CH_3, **26a** and **26b**), 4.68 (d, J = 10.0 Hz, 1H, CCHN (H-6a), **26a** and **26b**), 5.64 (d, J = 7.0 Hz, 0.09H, OCHO, (H-6), **26b**), 5.69 (s, 0.91H, OCHO, (H-4), **26a**), 6.70 (bs, 0.09H, NH, **26b**), 6.90 (bs, 0.91H, NH, **26a**); ^{13}C NMR(only the data for the major isomer **26a** are given): δ = 13.89 (q), 52.93 (d), 57.11 (q), 60.56 (d), 61.55 (t), 106.15 (d), 138.58 (s), 161.30 (s), 174.28 (s, C=O); HRMS calcd for $C_9H_{12}N_2O_5$: 228.075. Found 228.076.

2-Benzyl-3-carbethoxy-4-methoxy-1,3,3a,4,6,6a-hexahydro-furo[3,4-c]pyrrol-6-ones (28a-d)

A solution of 5-methoxy-2(5H)-furanone **1** (285 mg, 2.50 mmol), N-benzyl-ethylglycine **27** (965 mg, 5.00 mmol, 2 eq.) and p-formaldehyde (375 mg, 12.50 mmol, 5 eq.) in 25 mL toluene was stirred under reflux for 16 h under Dean-Stark conditions.[23] After cooling to room temperature, the solvent was evaporated and the residue purified by chromatography (silica gel, Et_2O). The products were separated by a second column chromatography (silica gel, hexane : ethyl acetate : Et_3N, 76 : 19 : 5) to afford three fractions (total amount 439 mg, 1.38 mmol, 55.0%). IR(pure): 1784 cm^{-1} (C=O (lactone)), 1734 cm^{-1} (C=O (ester)) **28a**: 0.133 g ^{1}H-NMR (300 MHz): δ = 1.20-1.30 (m, 3H, CCH_3), 2.80-3.88 (m, 6H, CCHC, CCH_2C), 3.45, 3.48 (s, s, 3H, OCH_3), 4.10-4.20 (m, 3H, CCHC, OCH_2C), 5.14-5.23 (s, d, 1H, OCHO, (H-4)), 7.22-7.38 (m, 5H, Ar, CH=CH), **28c, 28d**: 0.177 g ^{1}H-NMR (300 MHz): δ = 1.14-1.31 (m, 3H, CCH_3), 2.38-2.45 (m, 1H, CCHC), 2.93-3.86 (m, 5H, CCHC, NCHC, CCH_2C), 3.41, 3.42 (s, 3H, OCH_3), 4.01-4.30 (m, 3H, CCHC, OCHC), 5.07 (d, 0.52H, J = 2.20 Hz, OCHO, (H-4)), 5.10 (s, 0.04H, OCHO, (H-4)), 5.15 (d, 0.32H, J = 1.83 Hz, OCHO, (H-4)), 5.19 (d, 0.13H, J = 1.83 Hz, OCHO, (H-6)), 7.18-7.32 (m, 5H, Ar, CH=CH), ^{13}C-NMR (76.91 MHz): δ = 14.00-14.19 (t), 42.11 (d), 50.05 (d), 52.61-61.16 (d, t, t), 56.89 (q), 64.24-68.55 (t), 105.20-109.72 (d), 126.47-128.82 (d, Ar), 136.46-137.86 (s), 168.95-177.60 (s, s); **28b**: 0.129 g ^{1}H-NMR (300 MHz): δ = 1.21-1.31 (t, 3H, CCH_3), 2.86-3.94 (m, 6H, CCHC, NCHC), 3.54 (s, 3H, OCH_3), 4.06-4.21 (m, 3H, NCHC, OCHC), 5.42-5.48 (d, d, 1H, (H-6)), 7.16-7.31 (m, 5H, Ar, CH=CH); HRMS calcd for $C_{17}H_{21}NO_5$: 319.142. Found: 319.142.

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