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First examples of nitrile ylid cycloadditions to α,β-unsaturated lactones

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Abstract

We have investigated the 1,3-dipolar cycloaddition of several nitrile ylids to unsaturated five, six, and seven membered lactones. The cycloaddition proceeds effectively only with very electron-poor olefins. The α-methylene-γ-butyrolactone with an exocyclic double bond is the most reactive lactone. In all cases, *exo* adducts are obtained as major or exclusive products.

Keywords: nitrile ylids; cycloaddition; lactones

1. Introduction

1,3-Dipolar cycloaddition is one of the most powerful methods for the synthesis of five membered heterocyclic systems with varying degrees of unsaturations [1-3]. Easy access to and low cost of the dipoles, joined with simple reaction conditions, are some of the advantages of this reaction. Although a plethora of olefins have been employed as dipolarophiles, the use of unsaturated lactones is not very extensive and, as dipole partners only six types of 1,3-dipoles have been used: diazo compounds [4-10], nitrile oxides [5,6,11-15], nitrones [5,16-24], azomethine ylids [5,21,25-31], azides [32,33], and nitrilimines [34,35]. We have now studied the cycloadditions of some nitrile ylids to several unsaturated lactones. To the best of our knowledge, the results described herein are the first examples of such reactions.

2. Results and discussion

Starting with the imidoyl chlorides **1-3** (Figure 1), the corresponding nitrile ylids **4-6** were obtained *in situ* by elimination of hydrogen chloride with triethylamine. We have investigated the cycloaddition of dipoles **4-6** to the following lactones: γ-butyrolactone, **7**, β-angelica lactone, **8**, α-methylene-γ-butyrolactone, **9**, γ-methylene-γ-butyrolactone, **10**, α,β-pentenolide, **11**, and α,β-hexenolide, **12**. The selection of these lactones was made in order to study the influence of the ring size, to obtain information on the regio- and

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stereoselectivity of the cycloaddition, and to compare the reactivities of endo- *vs.* exocyclic and electron-rich *vs.* electron-poor double bonds.

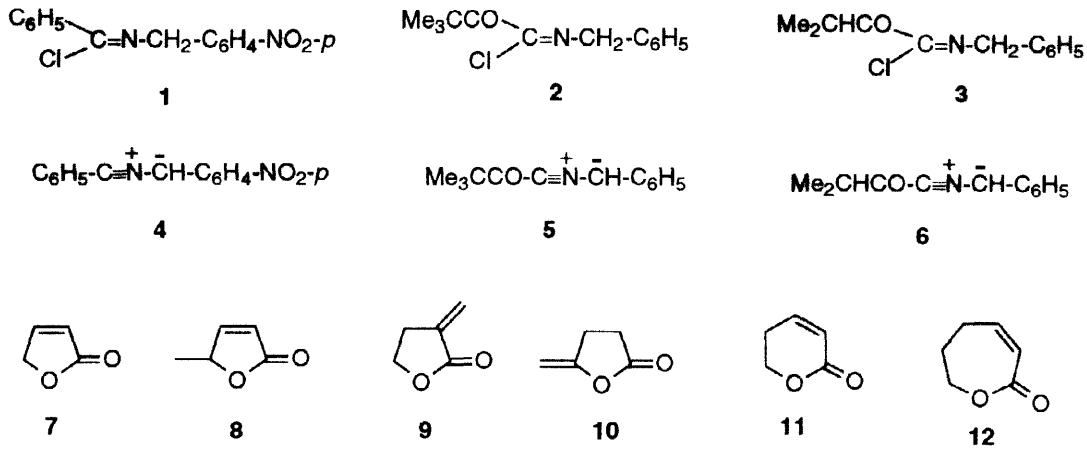
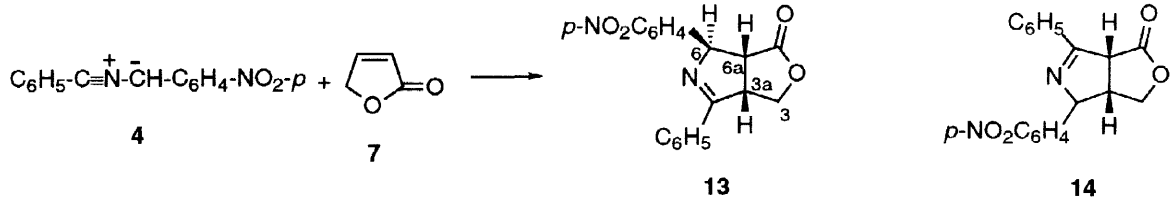


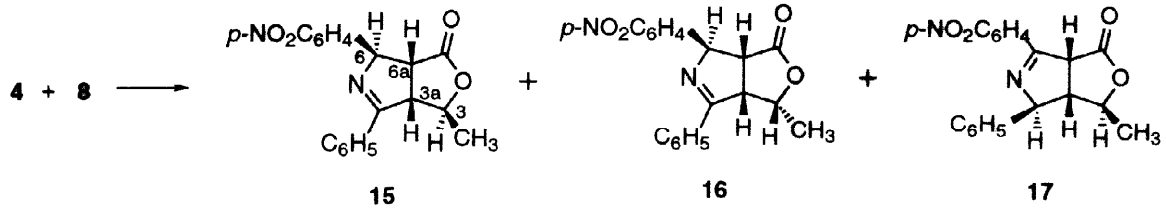
Figure 1

All the cycloadditions of dipole **4** were run in anhydrous benzene at room temperature. The reaction between **4** and **7** was completed after 40 h, and flash chromatography of the crude material afforded a sole cycloadduct **13** as a solid in 51% yield (Scheme 1). With the help of two dimensional NMR experiments we could assign all the proton and carbon atom absorptions of this compound and all the others described in this work. The regiochemistry of **13** was deduced from the COSY spectrum: the α-oxygen protons H_3 correlate with the multiplet at δ 4.45, attributed to H_{3a}, and this absorption correlates only with the signal at δ 3.40, assigned to H_{6a}. Irradiation of H_{6a} caused a 5.1% NOE on the *ortho* protons of the *p*-nitrophenyl ring. These observations allow us to discard the structure of the other possible regioisomer **14** and indicate that the hydrogen atoms at C_6 and C_{6a} are *trans* to each other. Consequently, adduct **13** derives from an *exo* transition state referred to the nitrophenyl ring of the dipole and the carbonyl group of lactone **7**. It is important to notice that the value of the coupling constant between H_6 and H_{6a}, which are in *trans* relationship, is small (3.1 Hz) compared to the observed $J_{3a,6a}$ and $J_{3cis,3a}$, both with values close to 9.5 Hz, according to a *cis* relative stereochemistry. These data will be decisive in the stereochemical assignment of other cycloadducts described later.

The cycloaddition between dipole **4** and lactone **8** (Scheme 2) was completed after 48 h, and flash chromatography of the crude material afforded a mixture of three cycloadducts, **15**-**17**, in a 6:2:1 ratio and 54% overall yield. Repeated column chromatography afforded pure **15** as a solid, a 1:1 mixture of **15** and **16**, and a small quantity of **17** in *ca.* 80% purity. For the major compound **15** the coupling constants $J_{3,3a}$ and $J_{6,6a}$ are small (2.5 Hz),



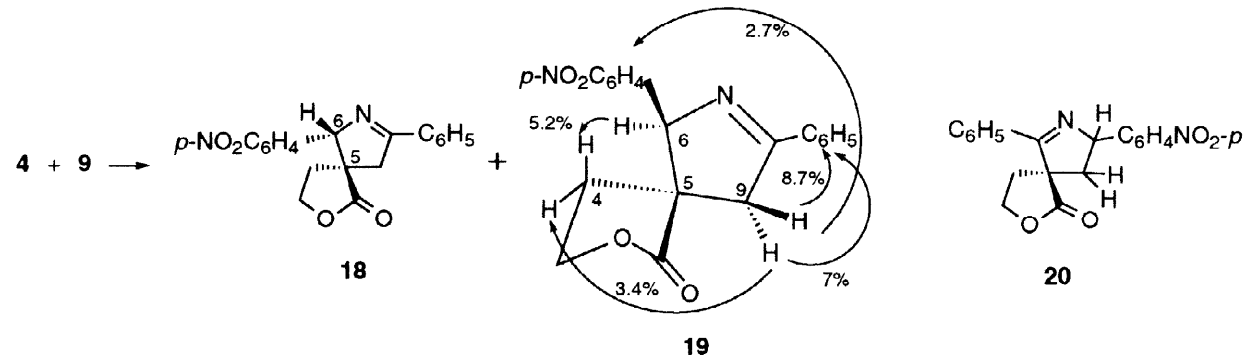
Scheme 1



Scheme 2

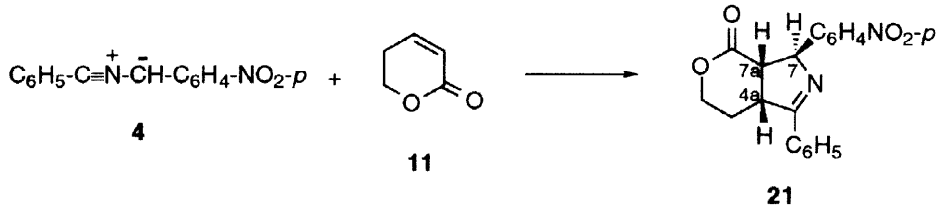
indicating a *trans* relationship between the corresponding protons. Therefore, this product derives from an *exo* transition state with an antifacial approach of the reactants. The value of $J_{3,3a}$=9.0 Hz in adduct **16** reveals that H_3 and H_{3a} are *cis* to each other, *i.e.* it results from a synfacial approach. Unfortunately, the value of $J_{6,6a}$=6.2 Hz did not allow to establish the relative stereochemistry of C_6/C_{6a}, but we assume it to be *trans* considering that an *endo-syn* transition state would be too sterically hindered [17,18,20,22-24]. The ^{1}H-NMR spectrum of **17** is significantly different from those of **15** and **16**. Protons H_{3a} and H_{6a} absorb at higher and lower field, respectively, than those of **15** and **16** and the chemical shifts of the aromatic protons are in agreement with the presence of an alkylsubstituted benzene ring and a *p*-disubstituted ring with two electron-withdrawing groups. These data match with the structure **17**, a tautomer of the pyrroline heterocycle. Regarding the stereochemistry, proton H_{3a} is *trans* to both H_3 and H_4 according to the small values of its coupling constants (4.1 Hz). We believe that **17** derives from a base catalyzed isomerization of the major adduct **15** caused by the triethylamine present in the reaction medium.

From the reaction between **4** and lactone **9** we could isolate compounds **18** (58%) and **19** (11%) as solids (Scheme 3). The presence in the ^{1}H-NMR spectra of both adducts of a singlet at δ *ca.* 5.6, assigned to H_6, is consistent with the proposed structures and discards the possible regioisomers **20**. The stereochemical elucidation of the minor adduct **19** is based on the following NOE experiments: i) presaturation of H_6 (δ 5.55) produces 5.2% enhancement of the signal at δ 2.66 corresponding to one of the hydrogen atoms at C_4; ii) irradiation of the signal at δ 3.18 (H_9) causes 7.0% NOE on the phenyl ring and 3.4% NOE on the other hydrogen atom at C_4 (δ 2.53); iii) when the other H_9 (δ 3.82) is irradiated the protons of both aromatic rings present NOE. The relative stereochemistry at C_5/C_6 of **18** should be the opposite and therefore the major adduct derives from an *exo* transition state.



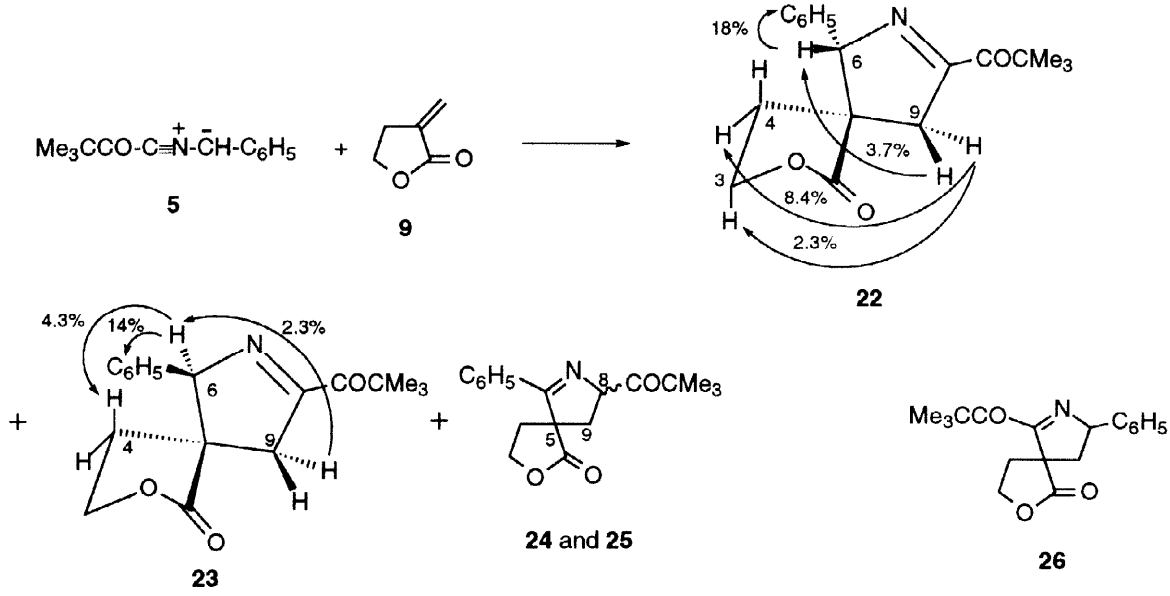
Scheme 3

Next we performed the reaction between **4** and the pentenolide **11** under the same conditions and isolated one cycloadduct, **21**, as a solid in 34% yield (Scheme 4). Its structure was evidenced by the double doublet at δ 3.22 presented by H_{7a}. The relative stereochemistry is assumed to be *exo* based on the former results.



Scheme 4

Attempted cycloadditions of nitrile ylid **4** to lactones **10** and **12** were unsuccessful. According to Sustmann's classification, nitrile ylids are nucleophilic dipoles of type I. In lactones **7**, **8**, **9**, and **11**, the reactive carbon-carbon double bond is conjugated to the carbonyl group, improving the dominating $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction. On the contrary, the double bond in lactone **10** is electron-rich, increasing the gap between the frontier orbitals and hence producing a lack of reactivity. The lower dipolarophilic activity of the seven membered lactone **12** may be related to the less efective conjugation of the unsaturated system, evidenced by the small chemical shift difference between its olefinic protons. Molecular model analysis reveals that the seven membered ring impedes the coplanarity of both double bonds. In fact, lactone **12** has already been shown to be less reactive than **7** and **11** towards nitrones [17,18].

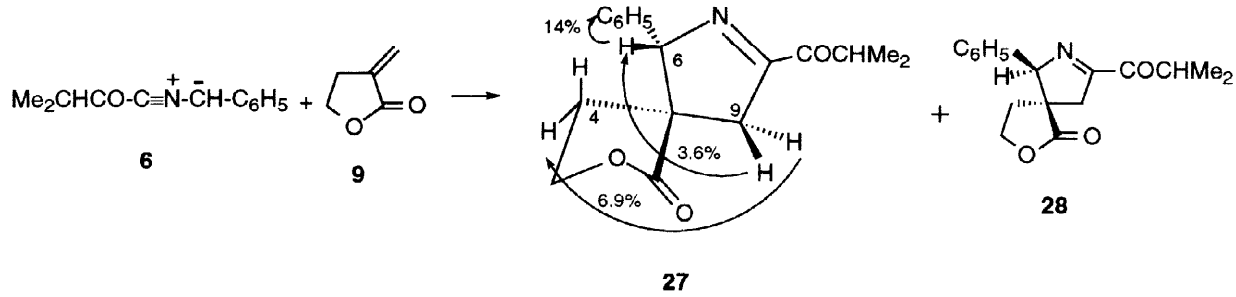


Scheme 5

The imidoyl chlorides **2** and **3** were also intended to react with lactones **7**, **8**, **9**, and **11** in the presence of triethylamine, but progress of the reaction was observed only when **9** was used as the dipolarophile. From the reaction between **5** and **9**, after several purifications by column chromatographies, we isolated four cycloadducts, **22-25**, in 60% overall yield

(Scheme 5). The spectroscopic data of **22** and **23** are very similar. The presence of a broad singlet around δ 5.7 in their ^{1}H-NMR spectra precludes the regioisomeric structure **26**. The relative stereochemistry of **22** and **23** was established by the indicated NOE experiments. Adduct **22** (22%) derives from an *exo* transition state, while compound **23** (19%) comes from an *endo* transition state. The ^{1}H- and ^{13}C-NMR spectra of **24** and **25** are similar to each other, but differ from those of **22** and **23**. In a HMBC experiment [36] performed with the major compound of the pair **24/25** the absorptions of the protons at C_9 (δ 2.35 and 2.57) correlate with the ketone group. The irradiation of proton H_8 (δ 5.52) produces no NOE enhancement on the aromatic protons. These data are only consistent with the proposed structures **24/25**. Unfortunately, since in both compounds the protons H_4 and H_9 are almost synchronous, the relative stereochemistry of these adducts could not be determined.

Compounds **27** and **28** could be isolated from the reaction between dipole **6** and lactone **9** in 18% and 8% yield, respectively (Scheme 6). The ^{1}H- and ^{13}C-NMR chemical shift values of both compounds correlate very well with those of **22** and **23**, allowing us to establish their structure. The observed NOEs demonstrate the *exo* stereochemistry of **27**, and by exclusion the *endo* of **28**.



Scheme 6

In summary, we describe the first cycloadditions of nitrile ylids to several unsaturated lactones. This study has revealed that high electron deficiency through an effective conjugation of the carbon-carbon double bond of the unsaturated lactone is necessary to have sufficient reactivity towards these dipoles. Dipoles **5** and **6** were less reactive than **4** and they only cycloadded to the most reactive lactone **9**, a terminal electron-poor olefin. In all these reactions, *exo* adducts are obtained as major or exclusive products.

3. Experimental section

Lactones **9** and **10** are commercially available. The following products were prepared according to previously described methods: **4** [37], **5** and **6** [38], **7** [39], **8** [40], **11** [41], and **12** [42,43]. Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 15-20 Torr. Flash column chromatography was performed using Merck silica gel (230-400 mesh). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AC-250-WB or AM-400-WB instruments in $CDCl_3$ solutions. Mass spectra were performed on a Hewlett-Packard 5985B instrument at 70 eV; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments.

*Cycloaddition of nitrile ylid **4** to 2(5H)-furanone, **7***

To a solution of imidoyl chloride **1** (389 mg, 1.41 mmol) and lactone **7** (154 mg, 1.84 mmol) in anhydrous benzene (2.1 mL) at room temperature under nitrogen atmosphere, a solution of triethylamine (270 μL, 1.96 mmol) in the same solvent (530 μL) was added during 1.5 h. The mixture was stirred at 20 °C for 40 h and the solid was filtered off. The solution was washed with 0.1 N HCl (3 x 1 mL) and water (1 mL). Flash chromatography of the crude material (478 mg) using hexane-ethyl acetate (1:2) as eluent afforded (3a*RS*,6*SR*,6a*SR*)-6-(4-nitrophenyl)-4-phenyl-3,3a,6,6a-tetrahydro-1*H*-furo[3,4-*c*]pyrrol-1-one, **13** (231 mg, 0.70 mmol, 51% yield): mp 150-153 °C (methylene chloride-pentane); IR (KBr): 1764, 1609, 1518, 1349, 1187 cm^{-1}; ^{1}H-RMN (400 MHz): δ 3.40 (dd, $J_{6a,3a}$=9.5 Hz, $J_{6a,6}$=3.1 Hz, 1H: H_{6a}), 4.45 (m, 1H: H_{3a}), 4.47 (dd, $J_{3,3}$=9.5 Hz, $J_{3,3a}$=3.1 Hz, 1H: H_3), 4.73 (t, $J_{3,3}$=$J_{3,3a}$=9.5 Hz, 1H: H_3), 5.82 (broad s, 1H: H_6), 7.40-7.60 (m, 5H), 7.78 (d, J=8.0 Hz, 2H), 8.13 (d, J=8.8 Hz, 2H); ^{13}C-RMN (62.5 MHz): δ 49.0 (C_{3a}), 51.0 (C_{6a}), 69.9 (C_3), 79.2 (C_6), 124.0/127.2/128.4/129.2/131.1/132.0/147.4/148.9 (C_{Ar}), 173.4 (CO), 177.4 (C=N); MS *m/z* 322 (M^+, 11), 278 (19), 277 (77), 238 (100), 192 (44), 165 (29), 89 (23). Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.95; H, 4.33; N, 8.63.

*Cycloaddition of nitrile ylid **4** to 5-methyl-2(5H)-furanone, **8***

To a solution of imidoyl chloride **1** (450 mg, 1.64 mmol) and lactone **8** (209 mg, 2.13 mmol) in anhydrous benzene (2.5 mL) at room temperature under nitrogen atmosphere, a solution of triethylamine (310 μL, 2.22 mmol) in the same solvent (610 μL) was added during 2.25 h. The mixture was stirred at 20 °C for 48 h and the solid was filtered off. The solution was washed with 0.1 N HCl (3 x 1 mL) and water (1 mL). Flash chromatography of the crude material (638 mg) using hexane-ethyl acetate (1:1) as eluent afforded a mixture of compounds **15**, **16**, and **17** (300 mg, 54% yield) in a ratio *ca.* 6:2:1, respectively. Repeated column chromatograpy using hexane-ethyl acetate (3:1) as mobile phase allowed the isolation of (3*RS*,3a*RS*,6*SR*,6a*SR*)-3-methyl-6-(4-nitrophenyl)-4-phenyl-3,3a,6,6a-tetrahydro-1*H*-furo[3,4-*c*]pyrrol-1-one, **15** (90 mg, 0.27 mmol, 16% yield), 10 mg of a 1:1 mixture of **15** and **16** and 3 mg of (3*RS*,3a*RS*,4*RS*,6a*SR*)-3-methyl-6-(4-nitrophenyl)-4-phenyl-3,3a,4,6a-tetrahydro-1*H*-furo[3,4-*c*]pyrrol-1-one, **17**, of *ca.* 80% purity. **15**: mp 115-117 °C (methylene chloride-hexane); IR (KBr): 3100, 3000, 2950, 1764, 1602, 1518, 1342, 1159 cm^{-1}; ^{1}H-RMN (250 MHz): δ 1.59 (d, J=6.4 Hz, 3H), 3.45 (dd, $J_{6a,3a}$=9.2 Hz, $J_{6a,6}$=2.5 Hz, 1H: H_{6a}), 4.03 (dt, $J_{3a,6a}$=9.2 Hz, $J_{3a,3}$=$J_{3a,6}$=2.5 Hz, 1H: H_{3a}), 4.74 (qd, J=6.4 Hz, $J_{3,3a}$=2.5 Hz, 1H: H_3), 5.80 (broad s, 1H: H_6) 7.40-7.60 (m, 5H), 7.81 (d, J=8.5 Hz, 2H), 8.16 (d, J=8.5 Hz, 2H); ^{13}C-RMN (62.5 MHz): δ 22.9 (CH_3), 51.3 (C_{6a}), 56.1 (C_{3a}), 78.8 (C_3), 79.1 (C_6), 124.0/127.2/128.3/129.1/131.5/131.9/147.4/148.9 (C_{Ar}), 173.1 (CO), 176.9 (C=N); MS *m/z* 336 (M^+, 13), 291 (53), 238 (100), 192 (43), 165 (25), 115 (20). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.85; H, 4.83; N, 8.32. **16** from the mixture of **15** and **16**: ^{1}H-RMN (250 MHz): δ 1.14 (d, J=6.6 Hz, 3H), 3.42 (dd, $J_{6a,3a}$=10.0 Hz, $J_{6a,6}$=6.2 Hz, 1H: H_{6a}), 4.58 (td, $J_{3a,6a}$=$J_{3a,3}$=9.0 Hz, $J_{3a,6}$=1.8 Hz, 1H: H_{3a}), 5.08 (dq, $J_{3,3a}$=9.0 Hz, J=6.6 Hz, 1H: H_3), 5.63 (broad d, $J_{6,6a}$=6.2 Hz, 1H: H_6), 7.40-7.50 (m), 7.50-7.60 (m), 7.65-7.75 (m), 8.10-8.20 (m). **17** (*ca.* 80% purity): ^{1}H-RMN (250 MHz): δ 1.51 (d, J=6.4 Hz, 3H), 2.97 (dt, $J_{3a,6a}$=8.9 Hz, $J_{3a,4}$=$J_{3a,3}$=4.1 Hz, 1H: H_{3a}), 4.60 (dd, $J_{6a,3a}$=8.9 Hz, $J_{6a,4}$=1.8 Hz, 1H: H_{6a}), 4.67 (qd, J=6.4 Hz, $J_{3,3a}$=4.1 Hz, 1H: H_3), 5.37 (broad d, $J_{4,3a}$=4.1 Hz, 1H: H_4), 7.30-7.50 (m, 5H), 8.15-8.25 (m, 4H).

*Cycloaddition of nitrile ylid **4** to 3-methylene-4,5-dihydro-2(3H)-furanone, **9***

To a solution of imidoyl chloride **1** (450 mg, 1.64 mmol) and lactone **9** (209 mg, 2.13 mmol) in anhydrous benzene (2.5 mL) at room temperature under nitrogen atmosphere, a solution of triethylamine (310 μL, 2.22 mmol) in the same solvent (610 μL) was added during 2 h. The mixture was stirred at 20 °C for 48 h and the solid was filtered off. The solution was washed with 0.1 N HCl (3 x 1 mL) and water (1 mL). Flash chromatography of the crude material (565 mg) using hexane-ethyl acetate (1:1) as eluent afforded the following fractions: i) 320 mg (0.96 mmol, 58% yield) of (5*RS*,6*RS*)-6-(4-nitrophenyl)-8-phenyl-2-oxa-7-azaspiro[4.4]non-7-en-1-one, **18**; and ii) 60 mg (0.18 mmol, 11% yield) of its (5*RS*,6*SR*)- isomer, **19**. **18**: mp 110-113 °C (methylene chloride-hexane); IR (KBr): 2924, 2854, 1764, 1609, 1511, 1448, 1349 cm^{-1}; ^{1}H-RMN (400 MHz): δ 1.75-1.85 (m, 2H: H_4), 3.35 (dd, $J_{9,9}$=16.5 Hz, $J_{9,6}$=1.5 Hz, 1H: H_9), 3.63 (dd, $J_{9,9}$=16.5 Hz, $J_{9,6}$=2.4 Hz, 1H: H_9), 3.79 (ddd, $J_{3,3}$=9.5 Hz, $J_{3,4}$=7.9 Hz, $J_{3,4}$=5.5 Hz, 1H: H_3), 4.13 (dt, $J_{3,3}$=9.5 Hz, $J_{3,4}$=$J_{3,4}$=7.3 Hz, 1H: H_3), 5.73 (broad s, 1H: H_6), 7.45-7.54 (m, 5H), 7.90 (d, J=8.9 Hz, 2H), 8.24 (d, J=8.9 Hz, 2H); ^{13}C-RMN (62.5 MHz): δ 31.4 (C_4), 48.0 (C_9), 53.9 (C_5), 65.6 (C_3), 80.0 (C_6), 124.2/128.1/128.5/129.1/132.0/133.2/146.5/148.1 (C_{Ar}), 172.4 (CO), 180.4 (C=N); MS *m/z* 336 (M^+, 27), 291 (37), 238 (100), 192 (54), 191 (23), 165 (34), 89 (24). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.83; H, 4.78; N, 8.28. **19**: mp 68-70 °C (methylene chloride-hexane); IR (KBr): 3065, 2924, 2854, 1764, 1623, 1518, 1349 cm^{-1}; ^{1}H-RMN (400 MHz): δ 2.53 (ddd, $J_{4,4}$=12.8 Hz, $J_{4,3}$=10.7 Hz, $J_{4,3}$=8.8 Hz, 1H: H_4), 2.66 (ddd, $J_{4,4}$=12.8 Hz, $J_{4,3}$=6.1 Hz, $J_{4,3}$=1.8 Hz, 1H: H_4), 3.18 (d, $J_{9,9}$=17.4 Hz, 1H: H_9), 3.82 (dd, $J_{9,9}$=17.4 Hz, $J_{9,6}$=1.8 Hz, 1H: H_9), 4.32 (td, $J_{3,3}$=$J_{3,4}$=10.7 Hz, $J_{3,4}$=6.1 Hz, 1H: H_3), 4.40 (td, $J_{3,3}$=$J_{3,4}$=9.4 Hz, $J_{3,4}$=1.8 Hz, 1H: H_3), 5.55 (broad s, 1H: H_6), 7.33 (d, J=8.5 Hz, 2H), 7.46-7.56 (m, 3H), 7.93 (d, J=8.9 Hz, 2H), 8.17 (d, J=8.5 Hz, 2H); ^{13}C-RMN (62.5 MHz): δ 37.2 (C_4), 45.8 (C_9), 53.7 (C_5), 64.9 (C_3), 84.2 (C_6), 124.0/128.3/128.7/129.1/132.1/133.0/145.3/148.2 (C_{Ar}), 174.6/177.7 (CO/CN); MS *m/z* 336 (M^+, 25), 291 (34), 238 (100), 192 (56), 191 (25), 165 (36), 105 (24), 89 (27). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.77; H, 4.71; N, 8.31.

*Cycloaddition of nitrile ylid **4** to 5,6-dihydro-2H-pyran-2-one, **11***

To a solution of imidoyl chloride **1** (483 mg, 1.76 mmol) and lactone **11** (224 mg, 2.28 mmol) in anhydrous benzene (2.6 mL) at room temperature under nitrogen atmosphere, a solution of triethylamine (330 μL, 2.37 mmol) in the same solvent (660 μL) was added during 1.75 h. The mixture was stirred at 20 °C for 20 h and the solid was filtered off. The solution was washed with 0.1 N HCl (3 x 1 mL) and water (1 mL). Flash chromatography of the crude material (600 mg) using ether as eluent afforded (4a*RS*,7*SR*,7a*SR*)-7-(4-nitrophenyl)-5-phenyl-1,3,4,4a,7,7a-hexahydropyrano[3,4-*c*]pyrrol-1-one, **21** (200 mg, 0.59 mmol, 34% yield): mp 152-155 °C (methylene chloride-pentane); IR (KBr): 3072, 2917, 1722, 1602, 1518, 1349 cm^{-1}; ^{1}H-RMN (250 MHz): δ 1.85 (m, 1H: H_4), 2.30 (m, 1H: H_4), 3.22 (dd, $J_{7a,4a}$=10.2 Hz, $J_{7a,7}$=7.0 Hz, 1H: H_{7a}), 4.04 (dddd, $J_{4a,7a}$=10.2 Hz, $J_{4a,4}$=$J_{4a,4}$=7.5 Hz, $J_{4a,7}$=2.0 Hz, 1H: H_{4a}), 4.20-4.35 (m, 2H: H_3), 5.60 (dd, $J_{7,7a}$=7.0 Hz, $J_{7,4a}$=2.0 Hz, 1H: H_7), 7.38-7.54 (m, 5H), 7.81-7.85 (m, 2H), 8.09-8.14 (m, 2H); ^{13}C-RMN (62.5 MHz): δ 26.3 (C_4), 46.1 (C_{4a}), 50.0 (C_{7a}), 66.6 (C_3), 78.4 (C_7), 123.8/127.6/128.3/128.7/129.0/131.7/147.3/149.9 (C_{Ar}) 171.1 (CO), 174.4 (C=N); MS *m/z* 336 (M^+, 64), 308 (16), 291 (100), 264 (52), 238 (57), 192 (63), 191 (33), 165 (55), 128 (36), 115 (37), 103 (24), 89

(49), 77 (32), 63 (36). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.70; H, 4.77; N, 8.30.

Cycloaddition of nitrile ylid ***5*** *to 3-methylene-4,5-dihydro-2(3H)-furanone,* ***9***

To a solution of triethylamine (660 μL, 4.70 mmol) and lactone **9** (503 mg, 5.13 mmol) in anhydrous acetonitrile (6.4 mL) at -10 °C under nitrogen atmosphere, a solution of imidoyl chloride **2** (1.01 g, 4.25 mmol) in the same solvent (4.4 mL) was added during 20 min. The mixture was stirred at 3 °C for 60 h and the solvent was removed. The residue was taken into methylene chloride and was washed with water (2 x 25 mL). Flash chromatography of the crude material (1.20 g) using hexane-ethyl acetate (3:1) as eluent afforded the following fractions: i) 45 mg of unidentified compounds; ii) 200 mg of (5*RS*,6*RS*)-6-phenyl-8-pivaloyl-2-oxa-7-azaspiro[4.4]non-7-en-1-one, **22**; iii) 100 mg of a *ca.* 6:1 mixture of **22** and 6-phenyl-8-pivaloyl-2-oxa-7-azaspiro[4.4]non-6-en-1-one, **24/25**; iv) 150 mg of **24/25**; v) 75 mg of a *ca.* 3:2 mixture of **24/25** and (5*RS*,6*SR*)-6-phenyl-8-pivaloyl-2-oxa-7-azaspiro[4.4]non-7-en-1-one, **23**; vi) 170 mg of **23**; and vii) 161 mg of a mixture of **23**, **25/24**, and **9** in a ratio *ca.* 2.5:1:5, respectively. Repeated column chromatography allowed a global isolation of 285 mg (0.95 mmol, 22% yield) of **22**, 241 mg (0.80 mmol, 19% yield) of **23**, 210 mg (0.70 mmol, 17% yield) of **24/25**, and 20 mg (0.07 mmol, 2% yield) of **25/24**. **22**: mp 111-113 °C (methylene chloride-pentane); IR (KBr): 2975, 1757, 1680, 1216, 1026, 941 cm^{-1}; ^{1}H-RMN (250 MHz): δ 1.37 (s, 9H: $3CH_3$), 1.68 (ddd, $J_{4,4}$=13.2 Hz, $J_{4,3}$=7.5 Hz, $J_{4,3}$=5.5 Hz, 1H: H_4), 1.80 (dt, $J_{4,4}$=13.2 Hz, $J_{4,3}$=$J_{4,3}$=7.5 Hz, 1H: H_4), 3.11 (dd, $J_{9,9}$=17.6 Hz, $J_{9,6}$=1.5 Hz, 1H: H_9), 3.32 (dd, $J_{9,9}$=17.6 Hz, $J_{9,6}$=2.2 Hz, 1H: H_9), 3.70 (td, $J_{3,3}$=$J_{3,4}$=8.0 Hz, $J_{3,4}$=5.5 Hz, 1H: H_3), 4.03 (q, $J_{3,3}$=$J_{3,4}$=$J_{3,4}$=7.5 Hz, 1H: H_3), 5.71 (broad s, 1H: H_6), 7.10-7.37 (m, 5H); ^{13}C-RMN (62.5 MHz): δ 26.8 ($3CH_3$), 31.7 (C_4), 44.2 ($C(CH_3)_3$), 48.7 (C_9), 52.7 (C_5), 65.8 (C_3), 82.6 (C_6), 127.1/128.2/128.8/137.1 (C_{Ar}), 169.9 (CN), 180.2 (CO), 204.3 (CO); MS *m/z* 299 (M^+, 17), 256 (12), 243 (14), 215 (13), 175 (55), 171 (39), 117 (32), 85 (28), 57 (100). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.20; H, 7.04; N, 4.73. **23**: mp 137-139 °C (methylene chloride-pentane); IR (KBr): 2973, 1755, 1682, 1173, 1014 cm^{-1}; ^{1}H-RMN (250 MHz): δ 1.35 (s, 9H: $3CH_3$), 2.42-2.55 (m, 2H: H_4), 2.97 (dd, $J_{9,9}$=18.1 Hz, $J_{9,6}$=2.0 Hz, 1H: H_9), 3.42 (dd, $J_{9,9}$=18.1 Hz, $J_{9,6}$=2.2 Hz, 1H: H_9), 4.07 (td, $J_{3,3}$=$J_{3,4}$=9.3 Hz, $J_{3,4}$=7.5 Hz, 1H: H_3), 4.19 (ddd, $J_{3,3}$=9.3 Hz, $J_{3,4}$=7.5 Hz, $J_{3,4}$=3.5 Hz, 1H: H_3), 5.38 (t, $J_{6,9}$=$J_{6,9}$=2.0 Hz, 1H: H_6), 7.10-7.18 (m, 2H), 7.27-7.36 (m, 3H); ^{13}C-RMN (62.5 MHz): δ 26.7 ($3CH_3$), 35.7 (C_4), 44.2 ($C(CH_3)_3$), 46.7 (C_9), 52.7 (C_5), 64.8 (C_3), 86.3 (C_6), 127.5/128.6/136.4 (C_{Ar}), 172.0/177.3 (CO/CN), 205.0 (CO). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.24, H, 7.22; N, 4.72. **24/25**: mp 86-87 °C (methylene chloride-pentane); IR (KBr): 2966, 2868, 1764, 1708, 1159, 1082 cm^{-1}; ^{1}H-RMN (250 MHz): δ 1.23 (s, 9H: $3CH_3$), 2.28-2.38 (m, 1H: H_4), 2.35 (dd, $J_{9,9}$=13.2 Hz, $J_{9,8}$=4.0 Hz, 1H: H_9), 2.57 (dd, $J_{9,9}$=13.2 Hz, $J_{9,8}$=8.4 Hz, 1H: H_9), 2.65 (dt, $J_{4,4}$=13.7 Hz, $J_{4,3}$=$J_{4,3}$=9.0 Hz, 1H: H_4), 4.20-4.40 (m, 2H: H_3), 5.52 (dd, $J_{8,9}$=8.4 Hz, $J_{8,9}$=4.0 Hz, 1H: H_8), 7.27-7.40 (m, 3H), 7.56-7.60 (m, 2H); ^{13}C-RMN (62.5 MHz): δ 26.2 ($3CH_3$), 34.7 (C_4), 39.6 (C_9), 44.2 ($C(CH_3)_3$), 59.7 (C_5), 66.5 (C_3), 74.3 (C_8), 128.1/128.6/130.7/131.9 (C_{Ar}), 171.8/178.7 (CO/CN), 212.8 (CO); MS *m/z* 300 (M^++1, 3), 299 (M^+, 2), 215 (69), 187 (23), 170 (44), 104 (38), 57 (100), 41 (36). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.14; H, 6.97; N, 4.66. **25/24**: IR (film): 2966, 2924, 2875, 1764, 1708, 1180, 1026 cm^{-1}; ^{1}H-RMN (250 MHz): δ 1.27 (s, 9H: $3CH_3$), 2.22 (ddd, $J_{4,4}$=13.3 Hz, $J_{4,3}$=7.2 Hz, $J_{4,3}$=3.1 Hz, 1H:

H_4), 2.30 (dd, $J_{9,9}$=13.0 Hz, $J_{9,8}$=7.0 Hz, 1H: H_9), 2.60 (dt, $J_{4,4}$=13.3 Hz, $J_{4,3}$=$J_{4,3}$=9.1 Hz, 1H: H_4), 2.71 (dd, $J_{9,9}$=13.0 Hz, $J_{9,8}$=9.0 Hz, 1H: H_9), 4.31 (td, $J_{3,3}$=$J_{3,4}$=9.1 Hz, $J_{3,4}$=7.2 Hz, 1H: H_3), 4.48 (td, $J_{3,3}$=$J_{3,4}$=9.1 Hz, $J_{3,4}$=3.1 Hz, 1H: H_3), 5.05 (dd, $J_{8,9}$=9.0 Hz, $J_{8,9}$=7.0 Hz, 1H: H_8), 7.30-7.45 (m, 3H), 7.67-7.72 (m, 2H); ^{13}C-RMN (62.5 MHz): δ 26.4 ($3CH_3$), 33.4 (C_4), 39.8 (C_9), 44.6 ($C(CH_3)_3$), 57.9 (C_5), 66.1 (C_3), 75.3 (C_8), 128.1/128.5/128.7/131.0 (C_{Ar}), 170.8/178.0 (CO/CN), 206.4 (CO).

Cycloaddition of nitrile ylid ***6*** *to 3-methylene-4,5-dihydro-2(3H)-furanone,* ***9***

To a solution of triethylamine (660 μL, 4.70 mmol) and lactone **9** (503 mg, 5.13 mmol) in anhydrous acetonitrile (6.4 mL) at -10 °C under nitrogen atmosphere, a solution of imidoyl chloride **3** (957 mg, 4.27 mmol) in the same solvent (4.4 mL) was added during 20 min. The mixture was stirred at 3 °C for 60 h and the solvent was removed. The residue was taken into methylene chloride and was washed with water (2 x 25 mL). Flash chromatography of the crude material (1.16 g) using hexane-ethyl acetate (3:1) as eluent afforded the following fractions: i) 217 mg (0.76 mmol, 18% yield) of (5*RS*,6*RS*)-8-isobutyryl-6-phenyl-2-oxa-7-azaspiro[4.4]non-7-en-1-one, **27**; ii) 101 mg (0.35 mmol, 8% yield) of its (5*RS*,6*SR*)- isomer, **28**; and iii) 100 mg of unidentified material. **27**: mp 91-93 °C (methylene chloride-pentane); IR (KBr): 2973, 2931, 2875, 1771, 1694, 1673, 1166, 1026 cm^{-1}; ^{1}H-RMN (250 MHz): δ 1.51 (d, J=6.9 Hz, 3H: CH_3), 1.56 (d, J=6.9 Hz, 3H: CH_3), 2.08 (ddd, $J_{4,4}$=13.0 Hz, $J_{4,3}$=7.5 Hz, $J_{4,3}$=5.5 Hz, 1H: H_4), 2.20 (dt, $J_{4,4}$=13.0 Hz, $J_{4,3}$=$J_{4,3}$=7.3 Hz, 1H: H_4), 3.47 (dd, $J_{9,9}$=17.7 Hz, $J_{9,6}$=2.0 Hz, 1H: H_9), 3.65 (dd, $J_{9,9}$=17.7 Hz, $J_{9,6}$=2.6 Hz, 1H: H_9), 4.05 (hept, J=6.9 Hz, 1H), 4.08 (ddd, $J_{3,3}$=9.2 Hz, $J_{3,4}$=7.7 Hz, $J_{3,4}$=5.5 Hz, 1H: H_3), 4.39 (dt, $J_{3,3}$=9.2 Hz, $J_{3,4}$=$J_{3,4}$=7.3 Hz, 1H: H_3), 6.05 (t, $J_{6,9}$=$J_{6,9}$=2.2 Hz, 1H: H_6), 7.50-7.55 (m, 2H), 7.65-7.75 (m, 3H); ^{13}C-RMN (62.5 MHz): δ 18.3 (CH_3), 18.4 (CH_3), 31.8 (C_4), 35.9 ($CHMe_2$), 46.7 (C_9), 53.4 (C_5), 65.8 (C_3), 82.3 (C_6), 127.1/128.4/128.9/136.8 (C_{Ar}), 170.5 (CN), 180.1 (CO), 202.8 (CO); MS *m/z* 285 (M^+, 40), 257 (8), 242 (6), 117 (34), 71 (100), 43 (75), 41 (20). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.57; H, 6.72; N, 4.92. **28**: mp 140-142 °C (methylene chloride-pentane); IR (KBr): 2973, 2931, 2875, 1757, 1694, 1209, 1173, 1012 cm^{-1}; ^{1}H-RMN (250 MHz): δ 1.13 (d, J=6.9 Hz, 3H: CH_3), 1.22 (d, J=6.9 Hz, 3H: CH_3), 2.41-2.55 (m, 2H: $2H_4$), 2.93 (dd, $J_{9,9}$=18.2 Hz, $J_{9,6}$=2.0 Hz, 1H: H_9), 3.46 (dd, $J_{9,9}$=18.2 Hz, $J_{9,6}$=2.2 Hz, 1H: H_9), 3.65 (hept, J=6.9 Hz, 1H), 4.08 (td, $J_{3,3}$=$J_{3,4}$=9.5 Hz, $J_{3,4}$=7.9 Hz, 1H: H_3), 4.20 (ddd, $J_{3,3}$=9.5 Hz, $J_{3,4}$=7.5 Hz, $J_{3,4}$=3.5 Hz, 1H: H_3), 5.37 (t, $J_{6,9}$=$J_{6,9}$=2.1 Hz, 1H: H_6), 7.10-7.15 (m, 2H), 7.25-7.35 (m, 3H); ^{13}C-RMN (62.5 MHz): δ 17.9 (CH_3), 18.6 (CH_3), 35.9 (C_4+$CHMe_2$), 44.7 (C_9), 53.5 (C_5), 64.9 (C_3), 85.8 (C_6), 127.4/127.7/128.7/136.0 (C_{Ar}), 172.3 (CN), 177.2 (CO), 203.0 (CO); MS *m/z* 285 (M^+, 8), 242 (3), 177 (42), 106 (21), 91 (100), 71 (29), 43 (37). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.43; H, 6.83; N, 5.04.

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