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CYCLOADDITION REACTIONS OF 1,2-DIAZEPINES WITH NITRILE OXIDES. SYNTHESIS OF 1,2,9-TRIAZA-8-OXABICYCLO-[5.3.0]-3,5,9-DECATRIENE DERIVATIVES

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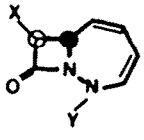
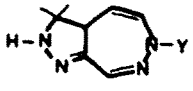
Abstract—A new heterocyclic system, 1,2,9-triaza-8-oxabicyclo-[5.3.0]-3,5,9-decatriene **4**, has been synthesized by regiospecific 1,3-dipolar cycloaddition of nitrile oxides to the imine double bond of 1,2-diazepines. Bis-adduct **5a** is obtained in only trace amounts showing that the imine double bond is more reactive than the Δ^4-olefinic bond.

1,2-Diazepines **3** which are easily obtained in preparative amounts by UV irradiation of 1-iminopyridinium ylides[1] are useful synthons for the construction of polycyclic systems, since their double bonds undergo various cycloaddition reactions. We have shown that ketenes, generated *in situ* from acetyl chlorides, react readily with 1,2-diazepines **3** to produce the corresponding β-lactams, **1**.[2] Furthermore, pyrazolino-diazepines are obtained by 1,3-dipolar cycloaddition of diazoisopropane to the Δ^4 bond of compounds **3**.[3] It therefore seemed appropriate to investigate the reactivity of 1,2-diazepines toward nitrile oxides. The latter undergo 1,3-dipolar cycloaddition with alkenes as well as with Schiff bases.[4]

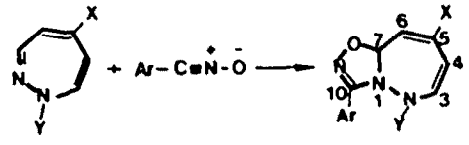


1



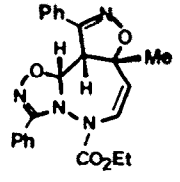
2

Initially we chose mesitylnitrile oxide since it does not dimerize to the corresponding furoxane at room temperature.[5] Reaction with various 1,2-diazepines gave high yields of 1:1-adducts whose structures were determined by ^{1}H and ^{13}C NMR spectroscopy. Protons H-3, H-4 and H-6 appear as vinylic hydrogens, unequivocally indicating cycloaddition to the Δ^2 bouble bond. In accord with a regiospecific cycloaddition process, only a single 1:1-adduct was obtained. Following Huisgen's 1,3-dipolar cyloaddition rule[6] which postulates a maximum gain in σ energy during cycloaddition, structures **4a–4d** have been assigned to the reaction products. This orientation is confirmed by ^{1}H and ^{13}C NMR spectroscopy. For example, the H-7 proton of compound **4c** appears at δ 6.03 ppm; a chemical shift of about δ 4.5 ppm would be expected for the reversed orientation. The ^{13}C NMR structure also agrees well with proposed structure **4c**. Thus C-7 appears as a doublet at δ 88.45 ppm, definitely excluding the alternative cycloadduct for which a chemical shift of about δ 50 ppm would be expected. Other characteristic ^{13}C NMR data for adduct **4c** are as follows: δ 112.60 (C-4; d), 131.87 (C-3; d), 132.54 (C-6; d) and 140.23 ppm (C-5; s). The 10 - mesityl - 1,2,9 - triaza - 8 - oxabicyclo - [5.3.0] - 3,5,9 - decatrienes represent a new heterocyclic system which can be obtained in *ca.* 60% yields from simple 4-substituted pyridines. 2:1-Cycloaddition products were not observed in the reaction of mesitylnitrile oxide with 1,2-diazepines.

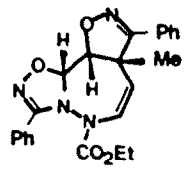


3 4

a) X = H , Y = $CO_2C_2H_5$
b) X = CH_3 , Y = $CO_2C_2H_5$
c) X = C_6H_5 , Y = $CO_2C_2H_5$
d) X = CH_3 , Y = COC_6H_5



5a



5b

We next turned our attention to benzonitrile oxide, prepared *in situ* from benzhydroxamic acid chloride.[7] Here too 1:1-adducts **4e–4g** were obtained, although in this case some dimerisation of benzonitrile oxide to 3,4-diphenylfuroxane was observed. In addition to the mono-adducts **4e**, reaction of diazepine **3b** with benzonitrile oxide gave trace amounts (3%) of a bis-adduct for which structure **5a** is proposed. The ^{1}H NMR

spectrum of this product clearly indicated cycloaddition to the Δ^2 and Δ^4 bonds, since H-4 appeared at δ 5.03 ppm (J = 9 Hz). This NMR data agree with those obtained from starting diazepine.[1] Protons H-9 and H-10 appear as doublets at δ 4.12 ppm and δ 5.83 ppm, respectively, with a coupling constant $J_{9,10} = 6$ Hz. Since the bis-adduct has three asymmetric centers, two of which are interrelated, two different stereoisomers are possible. According to the Karplus rule, the $J_{9,10}$ coupling constant of 6 Hz could correspond to either a dihedral angle of 40° or 130°. We first assumed initial front-side addition of benzonitrile oxide to diazepine **3b**, followed by backside addition of a second benzonitrile oxide molecule. In that case it is apparent from Dreiding models that two conformations **A** and **B** having H–C_9–C_{10}–H dihedral angles of 180° and 40°, respectively, are possible. In view of the $J_{9,10}$ coupling constant, conformation **A** must be discarded. The H–C_9–C_{10}–H dihedral angle of conformation **B** fits the observed coupling constant. However, severe non-bonding interaction would preclude attainment of this overcrowded conformation. If we assume that both benzonitrile oxide molecules undergo cycloaddition from the same side of diazepine **3b** two conformations are again possible, as observed with Dreiding models. Assuming N-1 to be partially sp^2-hydridized, both conformations have a H–C_9–C_{10}–H dihedral angle of approximately the same magnitude, 40–50°. Here again one conformation is more crowded than the other. The most likely conformation of bis-adduct **5a** is shown in Fig. 1.

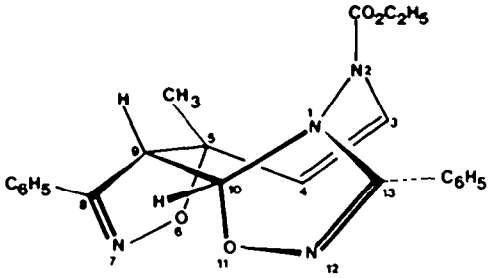


Fig. 1.

^{1}H NMR chemical shifts of the C-5 methyl and the H-9 proton in the bis-adduct rule out alternative structure **5b** which results from benzonitrile addition to the Δ^4 bond in an opposite sense to that of **5a**. If structure **5b** had been obtained, H-9 would appear at about δ 5 ppm and the C-5 methyl group at about 1.3 ppm.[8] On the other hand, for structure **5a** H-9 should appear at about δ 4 ppm and the C-5 methylgroup at about 1.7 ppm. Since the observed chemical shifts are 4.12 ppm and 1.85 ppm, structure **5a** is established.

Reaction of mono-adduct **4e** with a large excess of benzonitrile oxide did not lead to the expected bis-adduct **5a**. From this negative result it appears that benzonitrile oxide reacts with diazepine **3b** in two different ways. Mono-adduct **4e** is formed in a fast reaction, whereas mono-adduct **6** (not isolated) forms slowly but subsequently reacts rapidly with a second molecule of benzonitrile oxide to give the bis-adduct **5**.

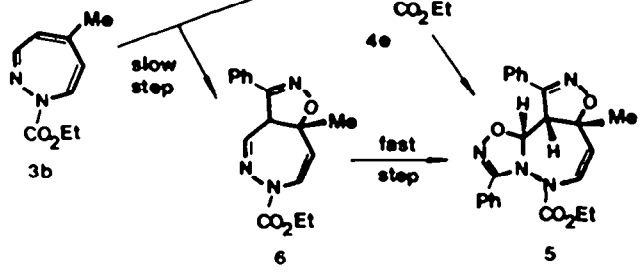
EXPERIMENTAL

Microanalyses were performed by the Service Central de Microanalyse of the C.N.R.S., divisions of Strasbourg and Lyon. M.ps were measured with a Tottoli apparatus (Büchi) and are corrected. IR spectra were determined with Beckman IR 20 A and Perkin–Elmer 157 G spectrophotometers. UV spectra were measured on a Beckman DB spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained with Varian A-60-A and T-60 and Varian XL-100/5 spectrophotometers, respectively in $CDCl_3$ solution, unless otherwise stated, using TMS as an internal standard (chemical shifts are given in δ values, s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet). Mass spectral measurements were performed on a Thomson 208 spectrometer at the Institut de Chimie of Université Louis Pasteur in Strasbourg. Column, thin and thick layer chromatography were carried out with silicic acid (Merck, Darmstadt). Solvents were reagent grade and distilled before use. 1,2-Diazepines were prepared photochemically from the corresponding 1-iminopyridinium yields in the standard way[1] using a dynamic thin film reactor.[9]

Cycloaddition reactions of 1,2-diazepines with mesitylnitrile oxide

(a) *Synthesis of* 2 - *ethoxycarbonyl* - 10 - *mesityl* - 1,2,9 - *triaza* - 8 - *oxabicyclo* - [5.3.0] - 3,5,9 - *decatriene* **4a**. A solution of 300 mg (1.8×10^{-3} mole) of 1-ethyoxycarbonyl - 1,2 - diazepine **3aa** and of 1.12 g mesitylnitrile oxide[10] (7.2×10^{-3} mole) in 10 ml anhydrous ether was stirred for 1 week at room temp. After removal of the solvent, the reaction mixture was separated by thick layer chromatography, eluting with an ethyl acetate-cyclohexane 2/8 v/v mixture. This procedure gave 240 mg of adduct **4a** as an oily compound (yield 50%) bp 70° (10^{-2} mm Hg; dec.); IR ($CHCl_3$) ν (C=O) 1740 cm^{-1}; UV (MeOH) λ (shoulder) 165 nm; ^{1}H NMR δ 1.23 (3H; t; J = 7 Hz); 2.23 and 2.33 (3 aromatic methyl groups); 4.16 (2H; q; J = 7 Hz); 5.06 (H-4; m); 5.62 (H-7; d; $J_{6,7} = 5$ Hz); 6.0 (2H; H-5 and H-6; m; $J_{4,5} = 5$ Hz); 6.50 (H-3; d; $J_{3,4} = 9$ Hz) and 6.80 ppm (2H, s); mass spectrum: *m/e* 327 (parent ion).

(b) *Synthesis of* 2 - *ethyoxycarbonyl* - 5 - *methyl* - 10 - *mesityl* - 1,2,9 - *triaza* - 8 - *oxabicyclo* - [5.3.0] - 3,5,9 - *decatriene* **4b**. A solution of 328 mg (1.82×10^{-3} mole) 1 - ethoxycarbonyl - 5 - methyl - 1,2 - diazepine **3b** and of 500 mg mesitylnitrile oxide (3.2×10^{-3} mole) in 30 ml ether gave, following procedure (a), and after crystallization from an ether–petroleum-ether mixture, 460 mg of adduct **4b** (yield: 72 mg) as a colourless crystalline compound; m.p. 122°; IR ($CHCl_3$) ν (C=O) 1730 cm^{-1}; UV



(MeOH) λ (shoulder) 262 nm (ε 5500) and λ (shoulder) 298 nm; ^{1}H NMR δ 1.22 (3H; t; J = 7 Hz); 1.90 (3H; s); 2.24 and 2.30 (3 aromatic methyl groups); 4.17 (2H; q; J = 7 Hz); 5.10 (H-4; d; $J_{3,4}$ = 9 Hz); 5.70 (H-6; m); 6.00 (H-7; m) 6.48 (H-3; d; $J_{3,4}$ = 9 Hz) and 6.85 ppm (2H; s); mass spectrum; *m/e* 341 (parent ion). (Calc. for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.1; H, 6.7; N, 12.0%).

(c) *Synthesis of* 2 - *ethoxycarbonyl* - 5 - *phenyl* - 10 - *mesityl* - 1,2,9 - *triaza* - 8 - *oxabicyclo* - [5.3.0] - 3,5,9 - *decatriene* **4c**. A solution of 242 mg (10^{-3} mole) 5 - phenyl - 1 - ethoxycarbonyl - 1,2 - diazepine **3c** and of 624 mg (4.10^{-3} mole) mesitynitrile oxide in 10 ml anhydrous ether gave, following procedure (a), and after crystallization from an ether–petroleum-ether mixture, 260 mg of adduct **4c** as colourless crystals (Yield 64%) m.p. 157°; IR (KBr disc) ν (C=O) 1750 cm^{-1}; UV (MeOH) λ (shoulder) 277 nm and λ (shoulder) 303 nm; ^{1}H NMR δ 1.27 (3H; t; J = 7 Hz); 2.25 and 2.35 (3 aromatic methyl groups); 4.20 (2H, q; J = 7 Hz); 5.48 (H-4; dd; $J_{3,4}$ = 9 Hz); $J_{4,6}$ = 1 Hz); 6.03 (H-7; m); 6.17 (H-6; m); 6.62 (H-3; d); 6.80 (2H; s) and 7.28 ppm (5H; s); ^{13}C NMR δ 19.6, 20.1 and 21.2 (CH_3 mesityl; q); 14.3 and 63.8 (ethyl); 88.5 (C-7; d); 112.6 (C-4; d); 126.8 (meta carbon of mesityl; d); 127.9, 128.6, and 128.7 (p- and o-carbons of phenyl, d); 131.9 (C-3; d); 132.5 (C-6; d); 137.6, 138.8 and 139.1 ppm (*p*-, *o*- and *o'*-carbons of mesityl; s); 140.2 (C-5; s); and 143.2 ppm (C-10; s). (Calc. for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.42. Found: C, 71.4; H, 6.2; N, 10.3%).

(d) *Synthesis of* 2 - *benzoyl* - 5 - *methyl* - 10 - *mesityl* - 1,2,9 - *triaza* - 8 - *oxabicyclo* - [5.3.0] - 3,5,9 - *decatriene* **4d**. A solution of 212 mg (10^{-3} mole) 1 - benzoyl - 5 - methyl - 1,2 - diazepine **3c** and of 624 mg mesitylintrile oxide (4 × 10^{-3} mole in 10 ml ether gave, following procedure (a) and after crystallization from an ether–petroleum-ether mixture, 230 mg of adduct **4d** (yield: 61%) as colourless crystals, m.p. 159°; IR (KBr) ν (C=O) 1665 cm^{-1}; UV (MeOH) λ (shoulder) 266 nm (ε 7,300) and λ (shoulder) 298 nm; ^{1}H NMR δ 1.95 (3 H; s); 2.05 and 2.25 (3 aromatic methyl groups); 5.08 (H-4; dd, $J_{3,4}$ = 9 Hz; $J_{4,6}$ = 1 Hz); 5.85 (H-6; m); 6.17 (H-7; m); 6.47 (H-3; d; $J_{3,4}$ = 9 Hz); 6.80 (2 H; s); and 7.30 ppm (5H; m); (Calc. for $C_{23}H_{22}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 74.0; H, 6.3; N, 11.3%).

Cycloaddition reactions of 1,2-*diazepines with benzonitrile oxide*

(e) *Synthesis of* 2 - *ethoxycarbonyl* - 5,10 - *diphenyl* - 1,2,9 - *triaza* - 8 - *oxabicyclo* - [5.3.0] - 3,5,9 - *decatriene* **4f**. To a solution of 242 mg (10^{-3} mole) 1 - ethoxycarbonyl - 5 - phenyl - 1,2 - diazepine in 15 ml diethyl ether, cooled to −15°, was added 1 ml triethylamine and then dropwise a solution of 780 mg (5 × 10^{-3} mole) benzhydroxamic acid chloride[7] in 5 ml dry ether. After 2 h the precipitated triethylamine hydrochloride was removed by filtration and the filtrate washed with a aqueous solution (pH 4) and then dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue chromatographed over silicic acid with ethylacetate/cyclohexane 2:8 (v/v). Besides diphenylfuroxane, 266 mg of unstable oil was isolated (yield: 62%); IR ($CHCl_3$), ν (C=O) 1730 cm^{-1}; UV (MeOH) λ (shoulder) 258 nm (ε: 7800); ^{1}H NMR δ 1.26 (3H, t; J = 7 Hz); 4.27 (2H; q; J = 7 Hz); 5.57 (H-4; dd; $J_{3,4}$ = 9 Hz; $J_{4,6}$ = 1 Hz); 6.10 (H-6; m); 6.20 (H-7; d; $J_{6,7}$ = 2 Hz); 6.68 (H-3; d; $J_{3,4}$ = 9 Hz) and 7.6 ppm (10 H; m); mass spectrum: *m/e* 361 (parent ion).

(f) *Synthesis of* 2 - *benzoyl* - 5 - *methyl* - 10 - *phenyl* - 1,2,9 - *triaza* - 8 - *oxabicyclo* - [5.3.0] - 3,5,9 - *decatriene* **4g**. A solution of 636 mg (3 × 10^{-3} mole) 1 - benzoyl - 5 - methyl - 1,2 - diazepine in 15 ml anhydrous ether was treated with 3 ml triethylamine and 2 g (1.3 × 10^{-2} mole) benzhydroxamic acid chloride in 10 ml dry ether following procedure (e). After chromatography 580 mg (yield: 58%) of adduct **4g** was isolated as an unstable oil: IR ($CHCl_3$) ν (C=O) 1690 cm^{-1}; UV (MeOH) λ shoulder 258 nm (ε: 9200); ^{1}H NMR δ 1.87 (3H; s); 4.17 (H-4; d; $J_{3,4}$ = 9 Hz); 5.73 (H-7,m); 6.03 (H-6; m); 6.50 (H-3; d; $J_{3,4}$ = 9 Hz) and 7.3 ppm (5H; m); mass spectrum *m/e* 331 (parent ion).

(g) *Synthesis of* 2-*ethoxycarbonyl*-5-*methyl*-10-*phenyl*-1,2,9 - *triaza* - 8 - *oxabicyclo* - [5.3.0] - 3,5,9 - *decatriene* **4e** *and of* 2 - *ethoxycarbonyl* - 5 - *methyl* - 8,13 - *diphenyl* - 1,2,7,12 - *tetraza* - 6,11 - *dioxatricycle* - [8.3.0.0^{4,9}] - 3,7,12 - *tridecatriene* **5**. A solution of 360 mg (2 × 10^{-3} mole) 1 - ethoxycarbonyl - 5 - methyl - 1,2 - diazepine **3b** in 10 ml dry ether was treated with 2 ml triethylamine and 1.56 g (10^{-2} M) hydroxamic acid chloride following procedure (e). After chromatography two compounds were isolated; adduct **4e**, 360 mg (yield 60%), as an unstable oil; IR ($CHCl_3$) ν (C=O) 1735 cm^{-1}; UV (MeOH) λ_{max} 261 nm (ε: 10,900); ^{1}H NMR δ 1.20 (3H; t; J = 7 Hz); 1.87 (3H; s) 4.18 (2H; q; J = 7 Hz); 5.14 (H-4; dd; $J_{3,4}$ = 9 Hz; $J_{4,6}$ = 1 Hz); 5.65 (H-6; m); 5.96 (H-7; m); 6.51 (H-3; d; $J_{3,4}$ = 9 Hz); 7.42 ppm (5H; m); mass spectrum: *m/e* 299 (parent ion); and bis-adduct **5**, 25 mg (yield: 3%) as a colourless crystalline product, m.p. 136°; IR (KBr) ν (C=O) 1735 cm^{-1}; UV (EtOH abs) λ (shoulder) 261 nm (ε: 12,600); ^{1}H NMR δ 1.03 (3H; t; J = 7 Hz); 1.87 (3H; s); 3.97 (2H; q; J = 7 Hz); 4.12 (H-9; d; $J_{9,10}$ = 6 Hz); 5.03 (H-4; d; $J_{3,4}$ = 9 Hz); 5.83 (H-10; d; $J_{9,10}$ = 6 Hz). 6.50 (H-3; d; $J_{3,4}$ = 9 Hz) and 7.48 ppm (10H; m); mass spectrum: *m/e* 418 (parent ion) (Calc. for $C_{27}H_{22}N_4O_4$: C, 66.01; H, 5.30; N, 13.51. Found: C, 66.0; H, 5.2; N, 13.4%).

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