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STEREOCHEMICAL STUDIES 113[1]
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CYCLOADDITION OF NITRILIMINE AND NITRILE OXIDE TO NORBORNANE- AND NORBORNENE-FUSED DIHYDRO-1,3-OXAZINES

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Abstract - By cycloaddition of nitrilimine and nitrile oxide to diexo and diendo norbornane- and norbornene-fused structural isomeric dihydro-1,3-oxazines (1-3), tetracyclic 1,3-oxazino-1,2,4-triazolines (7-9) and 1,2,4-oxadiazolines (10-12) were obtained. With norbornene dipolarophiles, which contain a C=N and a C=C bond, the cycloaddition takes place at the olefinic bond and the diexo compound 4 yields 13 regioselectively, whereas the diendo isomer 5 gives an isomeric mixture of isoxazolines 14 and 15. From the diexo derivative 6, however, a bis-adduct 16 is formed. The stereostructures of the adducts have been elucidated by NMR spectroscopy.

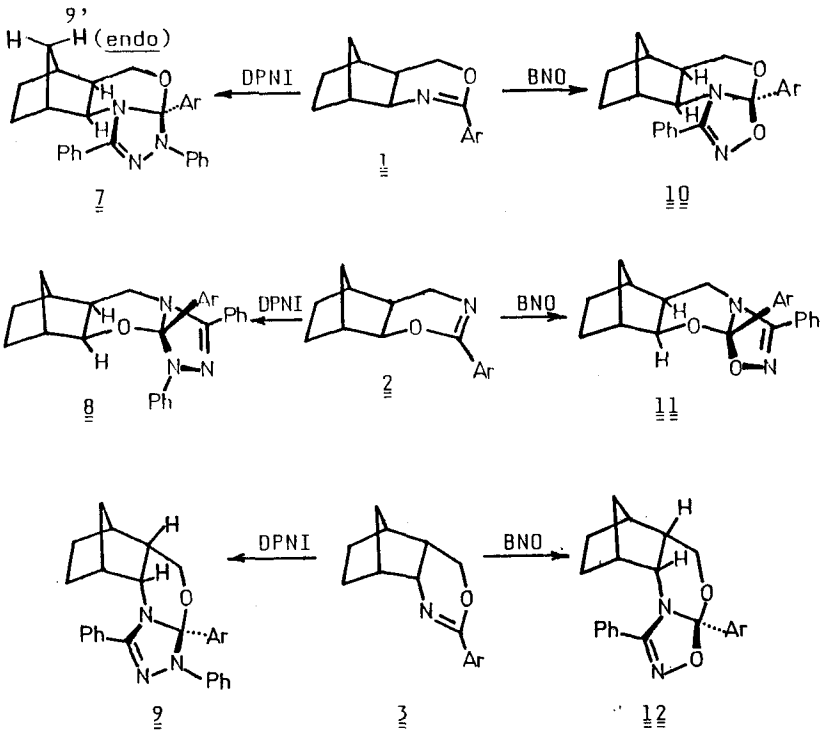
Our studies on saturated 1,3-heterocycles include the synthesis and structure elucidation of norbornane-1,3-oxazines and related compounds. In the cycloaddition of chloroacetyl chloride to the diexo and diendo norbornane- and norbornene-fused dihydro-1,3-oxazines (1-6),[3a,b,4] we found that angularly or linearly condensed tetracyclic azetidinone diastereomers were formed, which differed in the configuration of the carbon between the oxygen and nitrogen atoms.[5,6]

We now report cycloadditions involving dipolarophiles 1-6[3a,b,4] with diphenyl nitrilimine (DPNI) and benzonitrile oxide (BNO). In the cycloaddition with BNO, the norbornene-fused dihydro-1,3-oxazines 4 and 5 add the dipoles at the C=C bond only and the C=N bond does not take part in the reaction.

SYNTHESIS

The norbornane-fused dihydro-1,3-oxazine dipolarophiles (1, 3 and 5) were synthesized by the imidester cyclization of the corresponding aminoalcohols.[3a,b] The dipolarophiles 2 and 6, which are isomeric with respect to the positions of the heteroatoms, were prepared from norbornene or norbornadiene with hydroxymethylbenzamides.[7,8] Compounds 1-3 were reacted in dry benzene with DPNI generated *in situ* with triethylamine from N-(α-chlorobenzylidene)-phenylhydrazine, or in dry ether with BNO obtained with TEA from benzhydroxamic chloride. These reactions easily furnished the angularly fused diexo and diendo norbornane-1,3-oxazino-

1,2,4-triazolines (7 and 9) and 1,2,4-oxadiazolines (10 and 12), and the linearly fused analogues (8 and 11) as well (Scheme 1).



DPNI: $[PhC\bar{N}\text{-}\overset{+}{N}{=}CPh]$; BNO: $[PhC{\equiv}N{\rightarrow}O]$

10: Ar = $C_6H_4CH_3$-p; 2, 3, 7, 9, 11 and 12: Ar = C_6H_4Cl-p

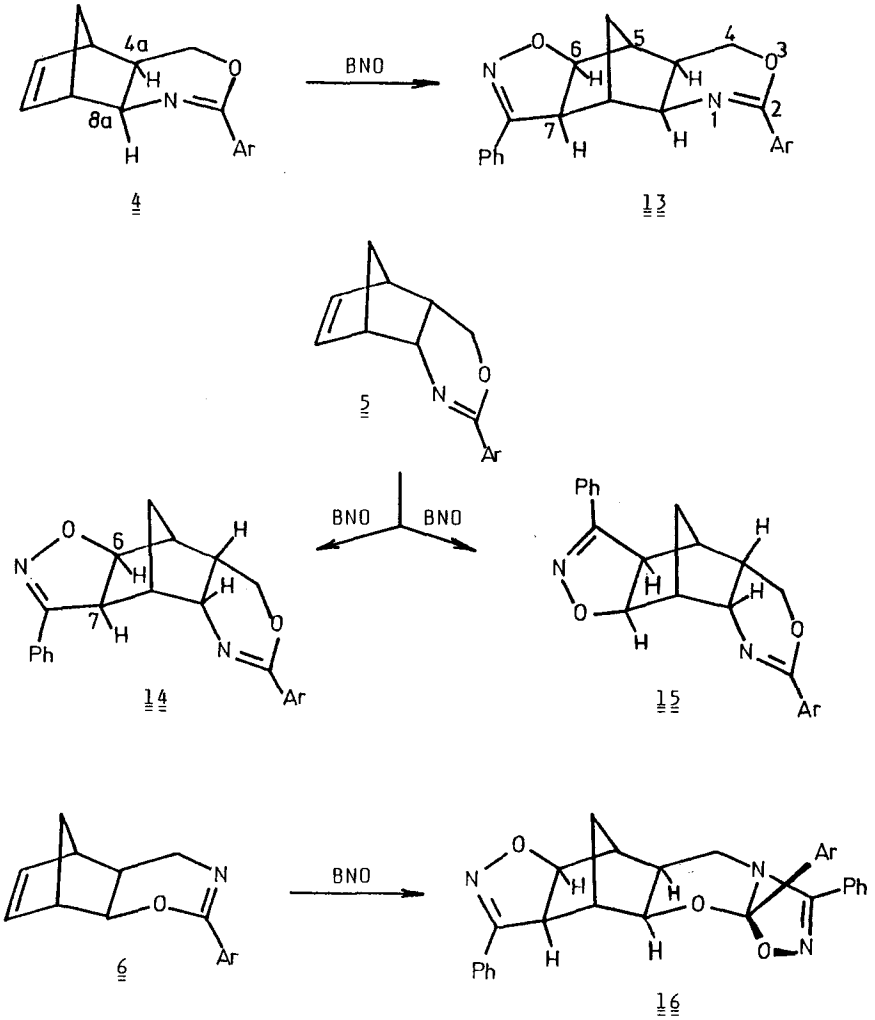
Scheme 1

The regioselectivity of 1,3-dipolar cycloadditions is known;[9a] in principle, a new heterocyclic ring can also be formed by hetero-hetero linkage at the C=N, but in the cycloadditions at hetero multiple bonds new carbon-hetero bonds of higher energy are always formed.[9b] Two further isomers can be expected, in which the configurations of the C-2 atom (the carbon between the oxygen and nitrogen atoms) are different. ^1H and ^{13}C NMR studies showed that the relative configuration of C-2 in 7-9 is R^*, whereas that in 10-12 is S^*, which indicates the cis fusion of the hetero rings and the endo position of the aryl substituent in 7, 9, 10 and 12, and its exo position in 8 and 11.[2] In 7, 9, 10 and 12, the oxazine ring has a chair-like conformation, and in 8 and 11 a boat conformation.[2] The structures of 9 and 12 were supported, among others, by the similar ^{13}C NMR chemical shifts of 9, 12 and 3. No steric compression shift was observed, indicating steric stress-less structures. In the case of exo 2-aryl substitution, a significant hindrance would act, for example, between H-7(endo) and the C-phenyl ring.[2]

The diexo annelation of the five-membered hetero ring in 7 and 10 was concluded from the considerable shift difference of the H-9'(endo) signals in the ^1H NMR spectra of these compounds. Similarly, the diendo-annelated five-membered hetero ring structure of 8 and 11 was based on the significantly different chemical shifts of the H-8a signals.[2]

In the DPNI cycloaddition of the norbornene dipolarophiles, adducts were formed which could not be isolated. The separation was more favourable in the cycloaddition of the double dipolarophiles 4-6 with BNO (Scheme 2). Here, however,

the expected 1,3-oxazino-1,2,4-oxadiazolines were not formed; instead, the dipole added mainly at the C=C bond, or in the case of 6 at both the C=N and C=C bonds.



4, 6, 13 and 16: Ar = C_6H_4Cl-p; 5, 14 and 15: Ar = $C_6H_4CH_3$-p

Scheme 2

The dipolarophile 4 furnished the tricyclic isoxazoline 13, in which the oxygen is linked to C-6. The constitution of 13 was proved by DNOE measurements. Saturation of the H-5 signal resulted in an increased intensity of the methine doublet of the >CH-O- moiety. The assignment of the H-5 or H-8 singlet followed from the NOE effect observed on the H-4a multiplet in the same experiment.[2] Besides this main product 13, a minor compound was also observed, but it could not be isolated. Regioselectivity was also found[10] in the cycloaddition of 2-substituted-7-oxanorbornenes.

The site-selectivity of the diendo double dipolarophile 5 is similar to that of 4, and the cycloaddition also took place only at the C=C bond. In the latter reaction, however, no regioselectivity was experienced: the two possible isoxazoline regioisomers (14 and 15) were formed in equimolar ratio, and could be separated. The structures of 14 and 15 were deduced from the smaller or higher shift difference, respectively, for the H-6,7 atoms relative to 5, where H-7 gives the downfield signal.[2] Structure 14 relates to the compound with m.p. 160-162 °C, and 15 to that with m.p. 171-173 °C.

In the case of the diexo dipolarophile 6, which contains the O and N hetero atoms in isomeric positions, the cycloaddition took place at the C=N as well as at the C=C bond, yielding the isoxazolinonorbornane-1,3-oxazino-1,2,4-oxadiazoline bis-adduct 16. Structure 16 is plausible because of the very similar NMR data of the half-molecule with the isoxazoline and oxadiazoline ring for 14 and 16 as well as for 11 and 16, respectively.[2]

For compounds 4 and 5, the higher reactivity of the C=C than of the C=N bond, i.e. the above-mentioned site-selectivity of the cycloaddition, can be explained by the presence of the bicyclo[2.2.1]heptene skeleton. It is known that the strain destabilizes the dipolarophiles, and hence the dipolarophile activity is increased.[9c] If the C=C bond is not situated in a methylene-bridged bicyclic skeleton, the site-selectivity is reversed. Decisive evidence is that with DPNI and BNO the related cis-2-p-tolyl-4a,5,8,8a-tetrahydro-4H-3,1-benzoxazine, which does not contain a norbornene structural unit, gives the 1,2,4-oxadiazoline monoadducts only, i.e. the cycloaddition takes place at the hetero multiple bond.[11] Further, with DPNI or BNO the 1-aza-1,3-butadiene, which has more than one true but conjugated dipolarophile site, reacted only at the more polar C=N bond, while the C=C bond remained intact.[12-15]

The site-selectivity, however, is influenced by steric factors as well. In the proximity of the annelation, the C=N bond of 4 is more hindered sterically than the hetero multiple bond in the dihydrooxazine ring of 6. This explains the formation of the monoadduct 13 from 4, in which the C=C bond is saturated, whereas the dipolarophile 6 gave the bis-adduct 16. Obviously, the steric hindrance is partly responsible for the fact that in the diendo dipolarophile 5 no cycloaddition took place at the C=N bond. In the monoadducts 14 and 15 formed in a sterically preferred reaction at the C=C bond, the hindrance of the C=N bond is much greater than in 6; therefore, a second addition, which would lead to a bis-adduct, is not possible.

The addition of the dipolarophiles 4-6 takes place exclusively on the exo face of the norbornene moiety and (in accordance with literature data[9d]) in each case diexo-isoxazolines (13-16) are formed at the C=C bond.

STRUCTURE

The spectroscopic elucidation of the stereostructure of compounds 7-16 will be reported in detail elsewhere.[2] The discussion here will be restricted to the presentation of the proved or probable structures, only mention being made of the spectroscopic principles and experimental methods used to elucidate the above structures.

Starting from the preferred conformation of the oxazine ring in 7, 10 and 9, 12, presumed on the basis of the values of the J(4,4a) and J(4',4a) couplings, the trans-annelation of the hetero rings can be excluded for steric reasons. Hence, of the two possible C-2 configurations in 9 and 12, only the endo one (containing the aryl group in the trans position of H-4a,8a) can be considered, which the 2R* (9) and 2S* (12) relative configurations suggest. (In the comparison of the NMR data, C-2 denotes the carbon between the three hetero atoms.) These stereostructures were supported by DNOE measurements.

For 7 and 10, assuming the probable conformation and cis annelation of the oxazine ring to the five-membered hetero ring, both feasible configurations of C-2 must be considered. Comparison of the ^{1}H NMR chemical shifts for the cycloadducts with those for the dipolarophile 1 strongly suggested the structure in which the aryl group is in the cis position to the H-4a,8a atoms, and thus the relative configurations of C-2 are probable R* (7) and S* (10).

The situation is similar for 8 and 11. With the conformations deduced from the coupling constants, and discarding the structures which can be ruled out for steric reasons, two stereostructures with different C-2 configurations remain to be distinguished. This was possible by utilizing the ^{1}H NMR shift differences between the starting molecule 2 and its cycloadducts 8 and 11, the DNOE measurements and the field effects in the ^{13}C NMR spectrum. These data give unambiguous evidence for the trans position of the aryl group and the H-4a,8a atoms, and hence the 2R* (8) and 2S* (11) relative configurations.

In 13-15, the saturation of the C=C and the presence of the C=N bond are obvious from the ^{1}H and ^{13}C NMR data. The saturation is clear from the lack of H-6,7 olefin proton signals; the incorporation of one 1,3-dipole molecule is proved by the appearance of the phenyl proton signals and the displacement of the C-6,7 signals from the region characteristic of unsaturated carbons to the aliphatic shift range, the practically unchanged C-2 shift and the appearance of phenyl carbon signals.

The diexo annelation of the isoxazoline ring follows from the doublet splitting of the H-6,7 signals: in the case of diendo annelation, these signals would appear as double doublets.[5,6] The structural isomers 13-15 can be distinguished through a comparison of their H-6,7 chemical shifts and those for the parent compound 5, and the same data prove the analogous structures of 13 and 14 as well.

From a comparison of the ^{1}H and ^{13}C NMR data for the bis-adduct 16 with those for the previously proved monoadducts 11 and 13, the structure of the former compound is obvious. The addition at the C=C bond resulted in the formation of a structure analogous to that of the monoadduct 13. On C=N addition the spectral data indicate the formation of a structure analogous to that of 11.

EXPERIMENTAL

IR spectra were run in KBr discs on a Bruker IFS-113v FT spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution in 5 and 10 mm tubes, at room temperature, on a Bruker WM-250 and WP-80-SY FT spectrometer at 250.13 (^{1}H) and 62.89 or 20.14 MHz (^{13}C), respectively, using TMS as internal standard. (For further details, cf. Ref.[2].)

Preparation of 1,2,4-triazolinomethanohexahydro-3,1- 7 and 9 and 1,3-benzoxazine 8

A mixture of dihydro-1,3-oxazine 1-3 (2.6 g; 0.01 mole), triethylamine (3 ml) and N-(α-chlorobenzylidene)-phenylhydrazine (2.3 g; 0.01 mole) in dry benzene (20 ml) was refluxed for 3 h. After cooling, the precipitate was removed by filtration. The filtrate was washed with water (3x10 ml) and dried (Na_2SO_4), and then evaporated to dryness. The residue was dissolved in benzene, transferred to a silica gel column, eluted with benzene and then with EtOH. The latter eluate was evaporated to dryness and the residue was crystallized from benzene—petroleum ether. The physical and analytical data on compounds 7-9 are listed in Table 1.

Preparation of 1,2,4-oxadiazolinomethanohexahydro-3,1- 10 and 12 and 1,3-benzoxazines 11, isoxazolinomethanotetrahydro-3,1-benzoxazines 13-15 and isoxazolino-1,2,4-oxadiazolinomethanohexahydro-1,3-benzoxazine 16

To a dry ethereal solution (20 ml) of dihydro-1,3-oxazine (2.4 g 1 or 5, 2.6 g 2-4 or 6; 0.01 mole) and triethylamine (1.0 g; 0.01 mole), chlorobenzaldoxime (1.6 g; 0.01 mole) in dry ether (10 ml) was added dropwise. After stirring at room temperature (1 h), the mixture was washed with water (2x10 ml), dried (Na_2SO_4), evaporated to dryness and in the case of 10 crystallized. In the other cases the oily or crystalline residue was transferred to a silica gel column and eluted with benzene and then with ethyl acetate. After evaporation of the benzene eluate, or in the case of 15 the ethyl acetate eluate, the residue was crystallized. Data on compounds 10-16 are given in Table 1.

Table 1. Physical and analytical data on compounds 7-16

Compd.	M.p. °C	Yield %	Found % C	H	N	Formula	Calculated % C	H	N
7	169-171[a]	53	73.60	5.71	9.25	$C_{28}H_{26}N_3ClO$	73.75	5.75	9.22
8	216-217[a]	65	73.56	5.61	9.17	$C_{28}H_{26}N_3ClO$	73.75	5.75	9.22
9	202-204[a]	61	73.89	5.80	9.20	$C_{28}H_{26}N_3ClO$	73.75	5.75	9.22
10	134-136[b]	80	76.52	6.54	7.70	$C_{23}H_{24}N_2O_2$	76.64	6.71	7.77
11	153-155[c]	49	69.16	5.60	7.43	$C_{22}H_{21}N_2ClO_2$	69.38	5.56	7.35
12	160-162[b]	57	69.17	5.50	7.31	$C_{22}H_{21}N_2ClO_2$	69.38	5.56	7.35
13	194-196[a]	52	69.82	5.17	7.51	$C_{22}H_{19}N_2ClO_2$	69.75	5.05	7.39
14	160-162[b]	35	77.30	5.91	7.91	$C_{23}H_{22}N_2O_2$	77.07	6.19	7.82
15	171-173[c]	32	77.21	6.00	7.84	$C_{23}H_{22}N_2O_2$	77.07	6.19	7.82
16	121-123[c]	64	70.25	4.99	8.51	$C_{29}H_{24}N_3ClO_3$	69.95	4.86	8.44

[a] From ethanol; [b] From ethyl acetate—petroleum ether; [c] From benzene—petroleum ether.

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