

Investigation of the site selectivity of 7-isopropylidene- and 7-(1-phenylethylidene)norbornadiene in 1,3-dipolar cycloadditions

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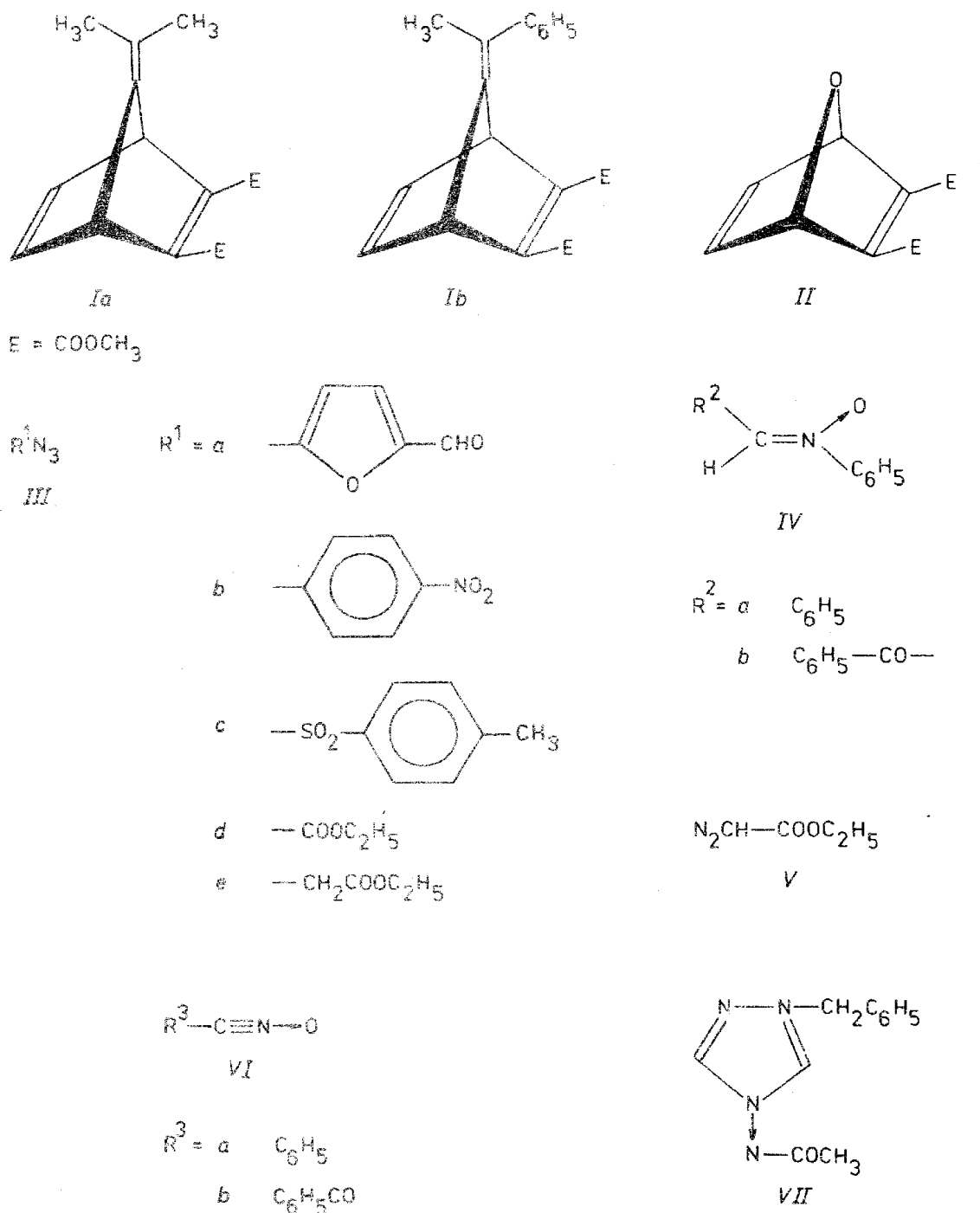
The site selectivity of 7-isopropylidene- and 7-(1-phenylethylidene)norbornadiene in 1,3-dipolar cycloadditions with *C,N*-diphenylnitrone, *C*-benzoyl-*N*-phenylnitrone, ethyl diazoacetate, azidoformate, ethylazidoacetate, 5-azido-2-furancarbaldehyde, *p*-nitrophenyl azide, tosyl azide, benzo- and benzoylnitrile oxide has been studied. The results are confronted with the site selectivity of 7-oxabicyclo[2,2,1]hepta-2,5-diene.

Изучалась "site selectivity" 7-изопропилиден- и 7-(1-фенилэтилиден)норборнадиена в реакциях 1,3-диполярного циклоприсоединения с *C,N*-дифенил- и *C*-бензоил-*N*-фенилнитроном, этиловым диазоацетатом, эфиром азидохлороуксусной кислоты, этилазидоацетатом, 5-азидо-2-фуранкарбальдегидом, *p*-нитрофенилазидом, тозилазидом, бензен- и бензоилнитрилоксидом. Результаты сравнивались с "site selectivity" 7-оксабицикло[2,2,1]гепта-2,5-диена.

In our earlier papers we have described the behaviour of 2,3-dimethoxycarbonyl-7-oxabicyclo[2,2,1]-2,5-heptadiene (*II*) towards various 1,3-dipoles [1—3]. In the present paper we report on 1,3-dipolar cycloadditions of 7-isopropylidene- (*Ia*) and 7-(1-phenylethylidene)norbornadiene (*Ib*) in order to assess the role of exocyclic double bond and confront it with that of oxygen in *II*.

Nonplanar structure of norbornadiene skeleton and the presence of two non-equivalent double bonds in *Ia*, *Ib* allows for the formation of two pairs of *exo* and *endo* isomers (Scheme 1). Literature data testify that in the majority of cases only *exo* adducts arise, e.g. with dienes [4, 5], 1,3-dipoles [1, 2, 6]. Only when an *exo* attack is blocked out by a bulky group a modicum of *anti* isomer has been observed [7—9].

FMO arguments lead to essentially the same results, since norbornadiene plays the role of HOMO component. Highest occupied molecular orbital in derivatives like *Ia*, *Ib* is localized on the 2,3-double bond with the *endo* part of the orbital partially blocked by the through space interaction, making the *exo* attack preferable. An *endo* attack becomes more feasible with halogen substituted norbornadienes due to the stabilization of LUMO in the cycloadditions with electron-rich dipoles, e.g. diazo derivatives reacting as HOMO component. It has further



Scheme 1

been found that substitution in positions other than 7 does not influence the *syn-anti* selectivity [10].

In derivatives *II*, *Ia*, *Ib* we encounter a different situation. Exocyclic double bond and oxygen are essentially symmetrical with respect to the two double bonds of norbornadiene. Electronic structure of the parent norbornadiene as well as that of 7-oxa analogue is known from MO calculations [11] and PES measurements

[12]. Interaction of the two double bonds causes splitting of energy levels of frontier orbitals HOMO and NHOMO. The gap between thus formed energy levels has been found to be 0.85 eV (PES method) in 7-oxabicycloheptadiene. In *II* its value has been estimated on the basis of the known IE and EA values of ethylene and dimethyl maleate to 0.5 eV [13]. Similar reasoning can be applied in the case of *Ia*, *Ib*. Frontier orbitals can now be localized on the respective double bonds, $(\pi_a - \pi_b)$ HOMO mainly on the unsubstituted, $(\pi_a^* + \pi_b^*)$ LUMO on the substituted double bond. "Localization" tallies with the relative size of orbital coefficients on both sites. Substituting oxygen in place of a CH_2 group as in *II* lowers the energy of LUMO by about 0.47 eV, in case of *Ia*, *Ib* one can expect similar, albeit less pronounced effect. In contrast to oxygen in *II*, the exocyclic double bond in *Ia*, *Ib* can mix its π orbitals with both substituted and unsubstituted double bond of the parent compound.

The majority of dipoles investigated in our study belong to electron-poor species, characterized by low lying LUMO and thus prone to attack *Ia*, *Ib* at their unsubstituted double bonds. Out of electron-rich 1,3-dipoles we have utilized *C,N*-diphenylnitrone. It reacted predominantly with the substituted double bond of *II* (Table 1), whereas *C*-phenyl-*N*-methylnitrone gave exclusively cycloadducts

Table 1

Site selectivity of *Ia*, *Ib*, and *II* in the reactions with 1,3-dipoles

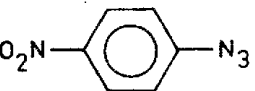
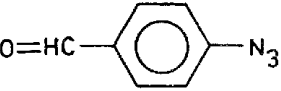
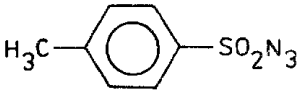
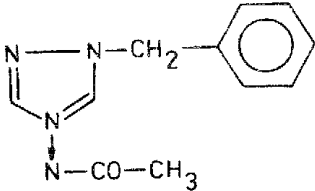
1,3-Dipole	Product amount of substance ratio: $\varphi = n_A : n_B$		
	<i>Ia</i>	<i>Ib</i>	<i>II</i>
$\text{Ph}-\text{CH}=\text{N}-\text{Ph}$ \downarrow O $\text{Ph}-\text{CO}-\text{CH}=\text{N}-\text{Ph}$ \downarrow O	—	—	2:1
$\text{N}_3\text{CH}_2\text{COOEt}$	0:100	0:100	52:48
N_3-COOEt	2:3	36:64	86:14
	0:100	0:100	35:65
	0:100	0:100	1:1
	0:100	0:100	57:43
$\text{N}_2\text{CH}-\text{COOEt}$	—	—	100:0
$\text{N}_2\text{CH}-\text{COOEt}$	100:0	100:0	97:3

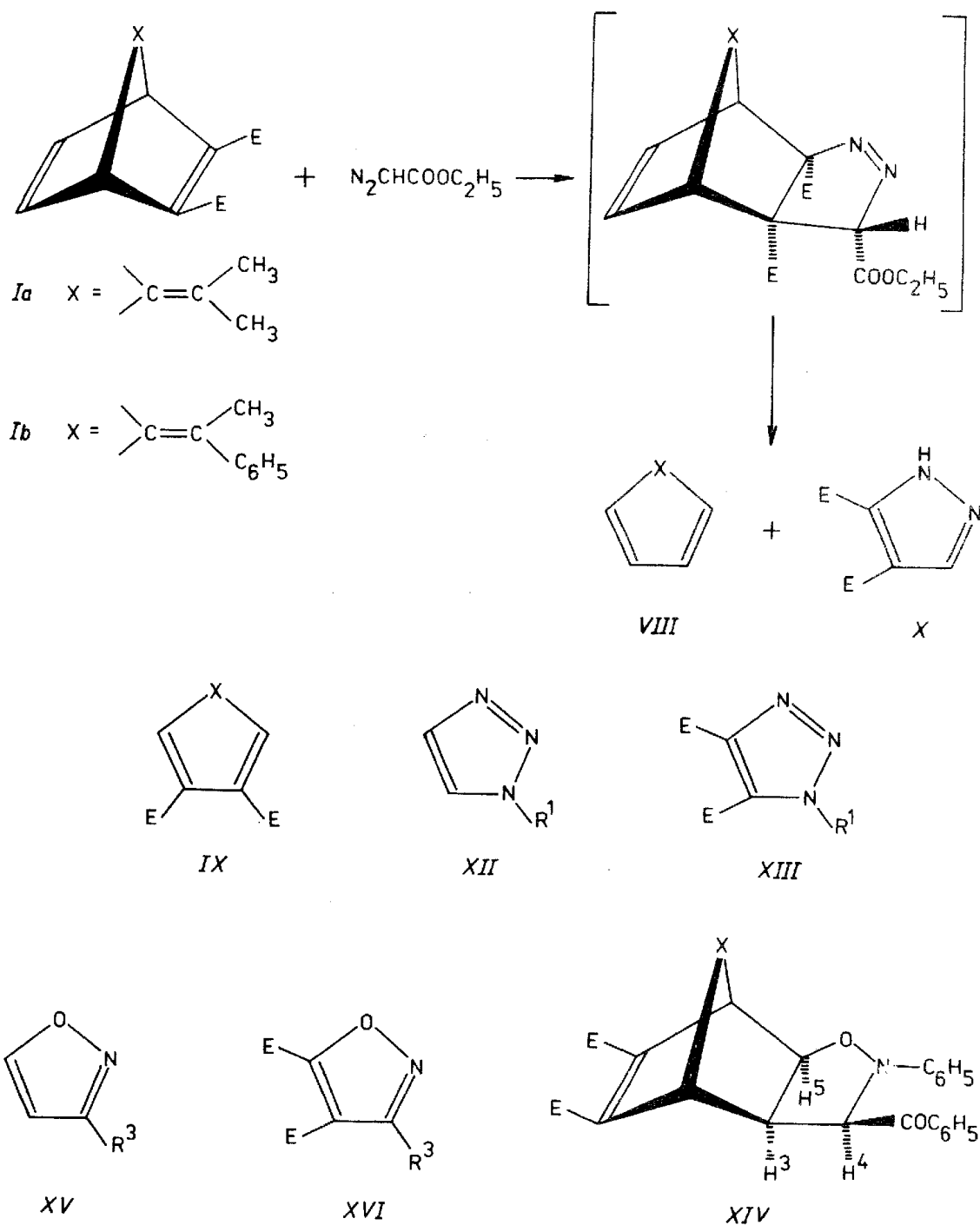
Table 1 (Continued)

1,3-Dipole	Product amount of substance ratio: $\varphi = n_A : n_B$		
	<i>Ia</i>	<i>Ib</i>	<i>II</i>
$\text{Ph}-\text{C}\equiv\text{N}\rightarrow\text{O}$	0:100	0:100	3:1
$\text{Ph}-\text{CO}-\text{C}\equiv\text{N}\rightarrow\text{O}$	—	—	55:45
	—	—	100:0

A — cycloaddition at the substituted double bond; B — substitution at the unsubstituted double bond.

on the substituted double bond of *II* in compliance with FMO theory arguments [13]. Exchanging *N*-methyl group by the phenyl group lowers LUMO energy, making LUMO(dipole)—HOMO(dipolarophile) interaction energetically favourable. Surprisingly *C,N*-diphenylnitrone failed to react with *Ia*, *Ib* in both polar (acetone) and nonpolar (benzene) solvents in temperature range 25–80 °C. Despite long reaction times no product formation could be detected. In the framework of FMO theory this can be accounted for by assuming energetically unfavourable FO interactions. Introduction of the benzoyl group in the nitrone moiety lowers LUMO energy to such an extent that LUMO(dipole)—HOMO(dipolarophile) interaction predominates, asserting itself in the exclusive formation of an adduct on the unsubstituted double bond. Nitrones not being the dipoles of the propargyl type, their cycloadducts are relatively stable and do not undergo cycloreversion under reaction conditions. Out of two possible diastereo isomers only *XIV* was formed (Scheme 2), having H-3, H-4, and H-5 in syn position. This configuration manifests itself in the typical signal splitting in their ¹H NMR spectra, analogous to that of *II*. Signal of the most deshielded H-3 proton can be found at $\delta = 4.8$ ppm as doublet ($J_{3,4} = 7$ Hz) in the spectra of both *XIVa* and *XIVb*, H-5 at $\delta = 4.7$ ppm ($J_{4,5} = 6$ Hz) in *XIVa* and $\delta = 4.1$ ppm in *IXVb*. H-4 signal appears at $\delta = 3.4$ ppm as apparent triplet, reducible to doublet by decoupling technique. Bridgehead protons H-6, H-9 display signals at $\delta = 3.9$ ppm as singlet for *XIVa*, the spectrum of *XIVb* shows overlapping signals of H-6, H-9 with those of methoxycarbonyl groups ($\delta = 3.75$ ppm). The shape of signals depends on solvent. In both cases (*XIVa*, *XIVb*) only one epimeric configuration on C-3 has been found to arise, in contrast to the reaction of *C,N*-diphenylnitrone with *II*, where both epimers were found [1].

Diazomethane is a member of group of electron-rich dipoles, the cycloadditions



Scheme 2

of which are governed by HOMO(dipole) interaction. In the cycloaddition with halogenated norbornadienes diazo derivatives like diazomethane, diazoethane, diphenyldiazomethane, 2-diazopropane have shown a tendency to form predominantly or exclusively *anti*—*endo* adducts [10]. With derivatives of the type *Ia*, *Ib* as well as with *II* diazo derivatives react at the substituted double bond in accord with the FMO theory, giving unstable cycloadducts, suffering cycloreversion to pyrazole and 4,5-dimethoxycarbonyl pyrazole. Interestingly ethyl diazoacetate

furnished essentially the same product distribution as 2-diazopropane. Only in the reaction with *II* a minor product of the reversed interaction has been formed [2].

Ethyl azidoacetate (*V*), a representative of the "second type" of dipoles [13], characterized by both types of FO interactions afforded in the reaction with *Ia*, *Ib* two triazoles, 1-ethoxycarbonylmethyl-1,2,3-triazole (*XII*) and 1-ethoxycarbonylmethyl-4,5-dimethoxycarbonyl-1,2,3-triazole (*XIII*). Both are formed by the cycloreversion of the primary unstable cycloadducts. Reaction with *Ia* furnished product amount of substance ratio $\varphi = 3:2$, *Ib* gave $\varphi = 2:1$ ratio with the predominating adduct at the unsubstituted double bond, indicating prevailing LUMO dipole interaction. Lowering its energy still more, as in ethyl azidoformate, HOMO dipole interaction ceases to assert itself and the cycloaddition leads exclusively to the corresponding 1-substituted triazole. Similar results were achieved with *II* [3].

Heteroaromatic azide (*IIIa*) behaved in the same manner giving in acetone 1-(5-formyl-2-furyl)-1,2,3-triazole as the sole product. This finding contrasts with the outcome of the reaction of *IIIa* with *II*, producing both triazoles with $\varphi = 1:1$ depending on solvent. Very good agreement between the quantitative FMO arguments and experimental data has been observed in the case of substituted phenyl azide. While 4-nitrophenyl azide gave almost exclusively cycloadditions on the unsubstituted double bond ($\varphi = 6:94$ for *Ia*) in accord with literature data [14], phenyl azide furnished, as expected, higher proportion of products arising from unsubstituted double bond ($\varphi = 17:83$). Similar trend has been observed with 2,3-dimethoxycarbonyl norbornadiene [14], *II* experienced comparable shift from 1:1 ratio for 4-nitrophenyl azide to the mixture with predominating 4,5-dimethoxycarbonyl triazole.

Stabilization of LUMO of phenyl azide by means of electronwithdrawing substituent, expected in the case of tosyl azide with the concomitant change in product distribution in favour of substituted double bond materialized only in the reaction with *II*. In the reaction with *Ia*, *Ib* tosyl azide proved recalcitrant partner, resisting reaction despite prolonged heating at 80 °C. Such lethargic rate of reaction has also been observed by Huisgen [15] in the reaction of tosyl azide with acetylene dicarboxylic acid dimethyl ester, successful only after 192 h of heating at 80 °C.

Benzonitrile oxide (*VIa*), a dipole of the propargyl type, reacted with *Ia*, *Ib* under formation of primary cycloadducts, which underwent subsequent aromatization to substituted isoxazole. By comparison with the authentic sample we have identified it as 3-phenylisoxazole. This finding is in good agreement with that of Cristina *et al.* [14], who found $\varphi = 1:9$ in favour of 3-phenylisoxazole. LUMO dipole interaction still prevailed in the reaction with 2,3-dimethoxycarbonyl norbornadiene, however with *II* the ratio is reversed to $\varphi = 3:1$ [2].

High rate of dimerization of benzonitrile oxide prevented us from learning

about its reactivity in cycloadditions with *I* under all attempted reaction conditions. Expected lowering of LUMO energy compared to phenyl analogue showed nevertheless in the reaction with *II*, where higher proportion of adducts on the unsubstituted double bond was found (from $\varphi = 1:3$ to $\varphi = 45:55$). Attempts to cyclize azomethineimine (*VII*) failed as well, due to its low reactivity, although it reacted smoothly with *II* to stable cycloadduct. Generally lower reactivity of *Ia*, *Ib* toward 1,3-dipoles as compared with that of norbornadienes and *II* can be rationalized, when additional orbital mixing is taken into account. In addition to through space interaction encountered in norbornadiene and *II*, homoconjugation of the exocyclic double bond in derivatives of the type *Ia*, *Ib* was being suggested and supported by both calculations [16] and experiments [17]. The homoconjugation demonstrated itself in the enhanced polarization of the exocyclic double bond, as seen from $\Delta\delta$ values in ^{13}C NMR spectra (C-7—C-8), $\delta = 41.7$ ppm for 7-isopropylidene norbornadiene and $\delta = 32$ ppm for 2,3-dimethoxycarbonyl-7-isopropylidene norbornadiene. In the latter case the exocyclic double bond is no longer symmetrical with respect to two other double bonds, resulting in different accessibility of *exo* and *endo* side in the reaction with singlet oxygen [17]. Consequently the unsubstituted double bond in *Ia*, *Ib* would be less accessible for an *exo* attack of 1,3-dipole, due to homoconjugation with C-7, C-8 exocyclic double bond, affecting mainly electroneficient dipoles like benzonitrile oxide, azomethineimine, and tosyl azide.

Experimental

Equipment used has been described in [2]. Benzonitrile oxide was prepared according to [18], tosyl azide according to [19], azidoformate and *C,N*-diphenylnitrone according to [2]. Azomethineimine used in the reaction was synthesized according to [20].

2,3-Dimethoxycarbonyl-7-alkylidenebicyclo[2,2,1]hepta-2,5-dienes *Ia*, *Ib*

A mixture of 2.8 g of acetylene dicarboxylic acid dimethyl ester (0.02 mol) and equimolar amount of 5,5-alkylidenefulvene was kept at 50 °C in benzene (10 cm³) for 16 h. After cooling separated crystals were removed by suction and washed with *n*-hexane. Yield = 3.5 g (71 %), m.p. = 89–100 °C for 7-isopropylidene derivative, Ref. [17] gives m.p. = 101 °C. ^1H NMR spectrum (CDCl_3), δ/ppm : 7.0 (s, 2H), 4.4 (s, 2H), 3.77 (d, 6H), 1.48 (s, 6H). Yield = 43 %, m.p. = 86 °C from methanol for 7-(1-phenylethylidene) derivative. ^1H NMR spectrum (CDCl_3), δ/ppm : 7.2 (m, 5H), 7.01 (d, 2H), 4.45 (d, 2H), 3.75 (d, 6H), 1.8 (s, 3H).

Cycloaddition of *C,N*-diphenylnitrone with *Ia*, *Ib*

Reaction mixture consisting of 0.2 g (1 mmol) of nitrone and 0.25 g (1 mmol) of *Ia*, or *Ib* was left to stand at 55 °C in CD_3COCD_3 for 24 h. After cooling tetramethylsilane was added and ^1H NMR spectrum of the reaction mixture measured. Results are given in Table 1.

Cycloaddition of C-benzoyl-N-phenylnitrone with Ia, Ib

A mixture of nitrone (1 mmol) and *Ia, Ib* (1 mmol) in 10 cm³ of dry ether is left to stand at laboratory temperature for 16 h. After evaporation yellow crystals remain (*XIVa*), or oily residue (*XIVb*). ¹H NMR spectrum (CD₃COCD₃), δ /ppm: *XIVa*: 1.5 (s, 6H), 2.1 (s, 6H), 3.45 (d, 1H), 3.76 (s, 6H), 4.2 (d, H-5, $J_{4,5}$ = 6 Hz), 4.4 (s, 2H), 4.8 (d, $J_{3,4}$ = 7 Hz), 7.0 (s, 2H), 7.5 (m, 10H); *XIVb*: 1.8 (s, 3H), 2.1 (s, 6H), 3.45 (d, 1H), 3.75 (m, 12H), 4.45 (d, 2H), 4.8 (d, 1H, $J_{3,4}$ = 7 Hz), 7.0—7.5 (m, 5H), over 7.5 (m, 10H).

Cycloaddition of ethyl diazoacetate with Ia, Ib

The reaction was carried out as with the *C*-benzoyl-*N*-phenylnitrone, reaction mixture analyses are in Table 1.

Cycloaddition of ethyl azidoacetate with Ia, Ib

Equimolar amounts of azidoacetate and *Ia, Ib* were left to react in 10 cm³ of dry ether for 20 h at laboratory temperature, ether was evaporated and the reaction mixture analyzed by ¹H NMR spectra. The reactions with azides were carried out in the same manner, cycloadditions with nitrile oxide *VIa* and *VIb* were effectuated according to [2].

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