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# A Study on the Reactions of Indol-3-yl-carbaldehyde Oximes with Electrophilic Alkenes/Alkynes. Generation of Nitrones from the O-H Oximes. 4π-Participation of the O-Me Oximes in Diels-Alder Reactions.

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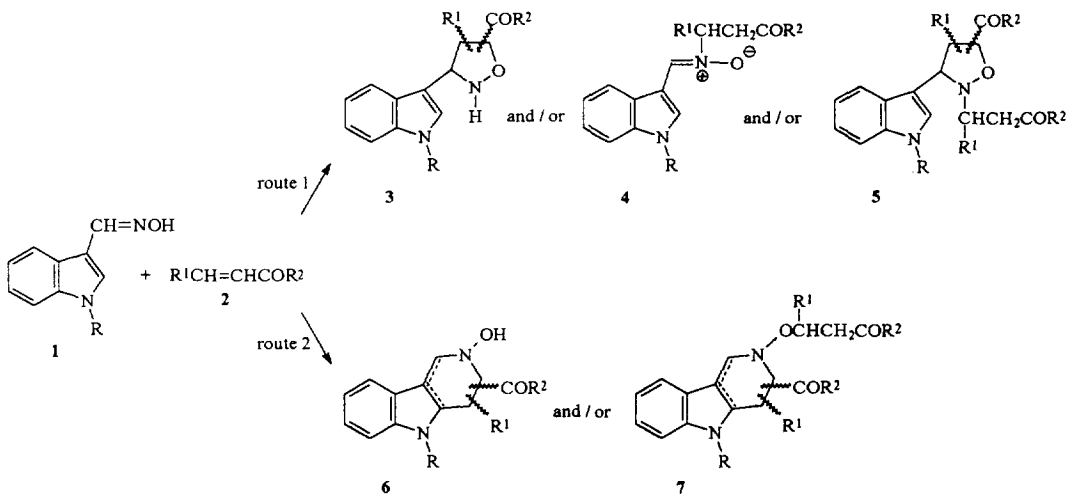
*Abstract* The reactions of indol-3-yl-carbaldehyde oximes with electrophilic alkenes/alkynes are studied. The O-H oximes **1** act as Michael donors towards the electrophilic reagent affording the isoxazolidines **9**, **10** through a tandem nitrone **8** generation - 1,3-dipolar cycloaddition process. The O-Me oximes **13** act as 1-aza-1,3-butadienes affording the γ-carbolines **16** and **19**. Copyright © 1996 Elsevier Science Ltd

Despite the fact that Diels-Alder reactions constitute a powerful tool for the constuction of a multitude of six-membered carbo- and heterocycles, only a limited number of α,β-unsaturated imine derivatives has been reported to have productive 4π-participation.[1] This is due to the inherent instability of the $\Delta^2$-piperideine products as well as to the poor reactivity of the 1-aza-1,3-butadienes which is ascribed to competitive activities (1,2-imine addition, imine tautomerism, conformational equilibria) that potentially preclude [4+2] cycloaddition. In the case of "inverse" electron demand reactions, the complementary N1 or C3 substitution of the 1-aza-1,3-butadienes with an electron-withdrawing substituent (acyl[2a-c] or sulfonyl[1b,2d,e,f]) accentuates their electron-deficient nature and facilitates their 4π-participation, thus extending the scope of the hetero-Diels-Alder reactions. In the case of "normal" electron demand reactions, the low reactivity of the 1-aza-1,3-butadiene, owing to the electron-withdrawing character of the nitrogen atom, has been to some extend overcome by the introduction of electron-releasing substituents. α,β-Unsaturated N,N-dimethylhydrazones[3a-f] and N-methyl-N-acylhydrazones[3g] have been proved to act inter- or intramolecularly as 1-aza-1,3-butadienes towards electron-deficient dienophiles. However, α,β-unsaturated oximes[4, 5] have been for a long time thought as non-productive 4π-heterodienes in [4+2] cycloadditions until the effective 4π-participation of 2-furfuraldoxime in intermolecular Diels-Alder reactions with electron-deficient alkenes was reported.[4] Except the normal Diels-Alder products, fused[2,3-c]pyridine derivatives, the Michael addition products of their N-hydroxy group to the electrophilic dienophile were also obtained. Almost at the same time, O-alkyl α,β-unsaturated oximes[5] were reported to be the 4π-participants in "normal" electron demand intramolecular [4+2] cycloadditions.

However, in the past few years, oximes, which are generally considered as potentially ambient nucleophiles, have been proved[6] to be the precursors of isoxazolidines in a wide range of tandem nitrone generation - 1,3-dipolar cycloaddition processes. An equilibrium of the oxime with the NH nitrone has been thought to be generated by 1,2-prototropy.[7] On the other hand, the nucleophilic addition of the lone pair of

the oxime to an electrophilic alkene (or alkyne[8]) or even to a non-activated alkene/alkyne[9,10] has been considered responsible for the generation of nitrones and designated as 1,3-azaprotio cyclotransfer reaction.[10]

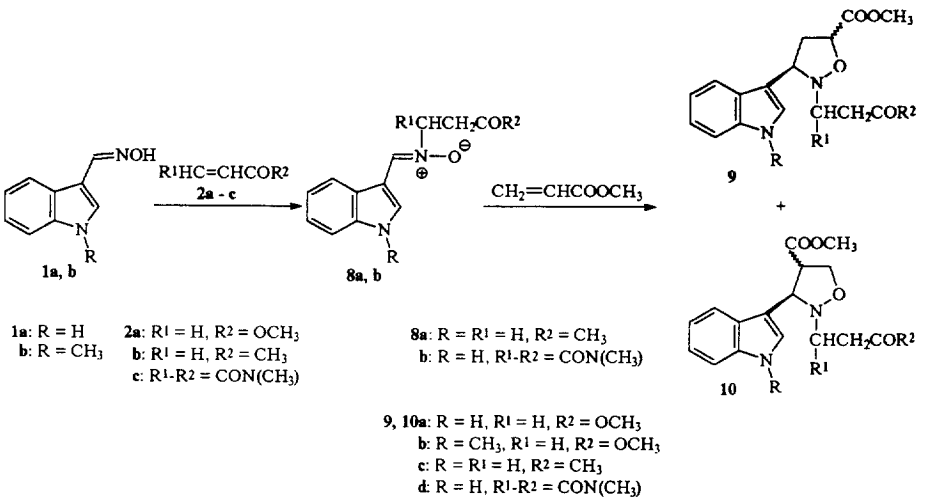
1-Ethoxycarbonylindole-3-carboxaldehyde N,N-dimethylhydrazone[11] is another 1-aza-1,3-butadiene with the C=C bond being part of an hetero-aromatic ring reported to participate in an intermolecular [4+2] cycloaddition reaction leading to an [a]annellated γ-carboline. Fused pyridoindoles have also been the intramolecular Diels-Alder products of properly N-substituted 3-formimidoylindoles.[12]




Scheme 1

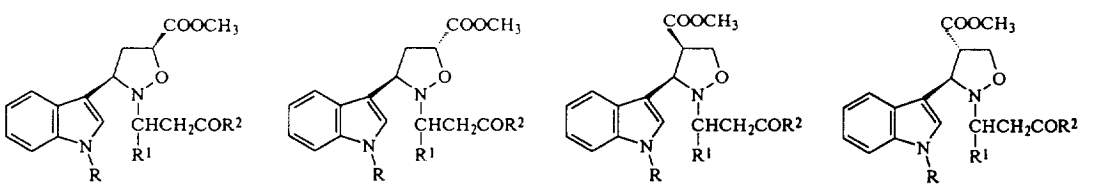
In connection with our interest to the synthesis of fused[b]indole derivatives[13] and intending to investigate the behaviour of indol-3-yl-aldoximes **1** towards electron-deficient alkenes/alkynes **2** we have undertaken and report herein the reactions of O-H and O-Me indol-3-yl-carbaldehyde oximes with electrophilic alkenes/alkynes. In the case that the oxime would act as 1,3-dipole precursor, products **3** and/or **4** and/or **5** (Scheme 1, route 1) would be expected to result, whereas in the case of an heterodiene behaviour the expected products would be **6** and/or **7** (Scheme 1, route 2).

The indol-3-yl- and 1-methylindol-3-yl-carbaldehyde oximes **1a** and **1b** were prepared according to literature methods[14,15] and were isolated as mixtures of E, Z isomers (~ 1 : 1.2 and 1 : 1.8 respectively) as it was indicated by their $^1$H NMR spectra. For the oxime **1a**, the separation of the mixture by column chromatography was unsuccessful leading to its enrichment to the more polar isomer. The reactions of the oxime **1a** with the electrophilic alkenes **2b,c** were performed in boiling benzene. The alkene has been used in excess (1 : 2.2 molar ratio) on purpose to act successively either as Michael acceptor and dipolarophile (Scheme 1, route 1) if the reaction might follow a nitrone intermediate **4** formation or as dienophile, to form an N-hydroxy-tetrahydro-γ-carboline **6** and Michael acceptor for the N-OH group of the intermediate product **6** (Scheme 1, route 2) if a Diels-Alder reaction would initially take place, in accordance with literature reports.[16, 4] In the case of **2a**, the reactions with the oximes **1a** and **1b** were carried out in the absence of solvent, using the alkene in greater excess.




Scheme 2

The reaction of **2a** with **1a** was quantitative and resulted in a mixture of four products, two diastereomeric 5-methoxycarbonyl-isoxazolidines $\mathbf{9a_1}$ and $\mathbf{9a_2}$ and two diastereomeric 4-methoxycarbonyl-isoxazolidines $\mathbf{10a_1}$ and $\mathbf{10a_2}$ (Scheme 2), in relative ratio 1.3 : 1. The stereoisomeric isoxazolidines $\mathbf{9a_1}$ and $\mathbf{9a_2}$ were separated after repeated column chromatographies, but this was not possible for the mixture of the isoxazolidines $\mathbf{10a_1}$ and $\mathbf{10a_2}$. Analogous products, the isoxazolidines $\mathbf{9b_1}$, $\mathbf{9b_2}$ and $\mathbf{10b_1}$, $\mathbf{10b_2}$ were also obtained quantitatively, in relative ratio ~ 1.4 : 1, from the reaction of **1b** with methyl acrylate. In this case too, the separation of the isoxazolidines $\mathbf{10b_1}$ and $\mathbf{10b_2}$ was unsuccessful. From the 5-substituted isoxazolidines **9b** only $\mathbf{9b_2}$ was practicable to be separated whereas $\mathbf{9b_1}$ was characterized from its mixture with $\mathbf{10b_1}$ and $\mathbf{10b_2}$.




The structure elucidation of the products was based on their spectroscopic and analytical data. The molecular ion peaks in the mass spectra of all the products indicate a proportion: alkene / oxime = 2 : 1. Furthermore, in the $^1$H NMR spectra of compounds **9** and **10** signals due to the indole ring 2-H can be recognized at δ 7.10-7.20. This token accompanied by the absence of any two protons signal corresponding to a $OCH_2$ group gives further support to the proposed structures and excludes any structure of type **7** ($R^1$=H). The assignment of the regiochemistry of the cycloadducts **9** and **10** was readily approached by comparison of their $^1$H and $^{13}$C NMR spectra with that of other known isoxazolidines.[13a, 16] In more details, for the isolated 5-substituted regioisomers **9**, the 4-, 3- and 5- isoxazolidine protons appear at δ 2.59-2.96, 4.05-4.23 and 4.69-4.76 respectively whereas for the 4-substituted regioisomers the resonances of the 4- and 3-, 5-H appear at δ

3.48-3.88 and 4.14-4.60. In the $^{13}C$ NMR spectra of the 5-substituted isomers **9** characteristic peaks for the C-4, C-3 and C-5 of the isoxazolidine ring can be distinguished at δ 33.1-33.2, 63.0-63.8 and 74.3-75.1. The C-4 and C-3, C-5 of the 4-substituted isomers **10** resonate at δ 52.1-52.7 and 66.0-68.4 respectively. A remarkable feature that characterizes the $^1H$ NMR spectra of **10a** and **10b** and strongly supports the structures proposed for them is the shielding of one methoxy group, the 4-$COOCH_3$ of the *cis* stereoisomers $\mathbf{10a_1}$ and $\mathbf{10b_1}$ (δ 3.01 and 3.03 respectively) which has already been pointed out for other analogous isoxazolidines.[13a, 16] The $^1H$ and $^{13}C$ NMR (recorded at 300 MHz and 75.5 MHz respectively, at 25 °C) of the isoxazolidines **9** and **10** reveal dynamic effects, possibly due to the isoxazolidine nitrogen inversion[13a, 17] indicated by line broadening of some signals. On recording the spectra at higher temperature, the broads get sharper. Thus, in the spectrum of $\mathbf{9a_2}$ (25 °C) the broad signals for the 3-H and N-$CH_2$ (two peaks at δ 3.17, 3.21) appear as triplet and two multiplets respectively at 50 °C. By analogy, the broad low intensity signals at δ 40.5 and 63.0 (25 °C), corresponding to C-4 and C-3, become narrower and more intense (50 °C) whereas another broad at δ 52.0 (for the N-$CH_2$) remains almost unchanged.

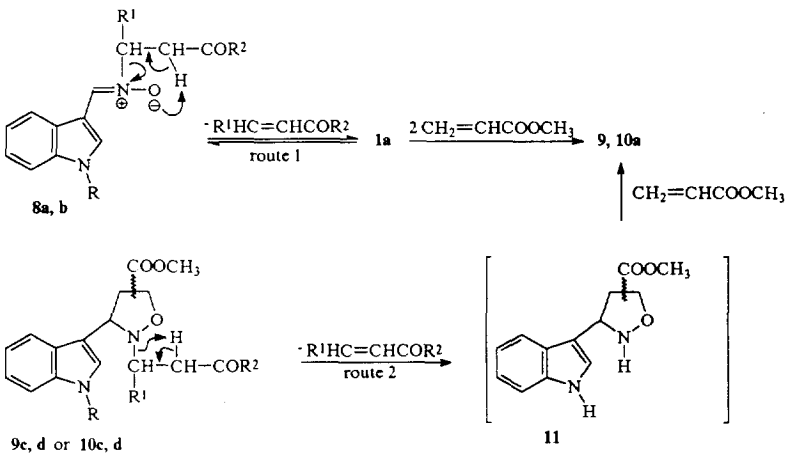
Concerning the stereochemical assignment of the 5-substituted isomers **9**, for lack of other evidence, it was just relied upon the observations of Grigg[16] who notes that the differences in chemical shift (Δδ) of the two 4-methylene protons as well as that of the 3-H and 5-H of analogous isoxazolidines are both greater in the *cis* than in the *trans* isomer. In our case the differences in chemical shifts mentioned for the isomers $\mathbf{9a_1}$ and $\mathbf{9a_2}$ are measured as follows: $\mathbf{9a_1}$; Δδ (4-H) = 0.19, Δδ (3-H / 5-H) = 0.64. $\mathbf{9a_2}$; Δδ (4-H) = 0.11, Δδ (3-H / 5-H) = 0.54. However, some reservations are retained, concerning the chemical shifts of 3-H, because of the broadening of the corresponding signals, due to the dynamic effects mentioned above.

More evidence about the structure of product **10a** (mixture of stereoisomers), which exhibits strong absorptions at 3380 $cm^{-1}$ in the IR spectrum has come from its methylation carried out with methyl iodide and potassium hydroxide in DMF. The appearance in the $^1H$ NMR spectrum of the methylation product of two additional singlets with associated chemical shifts (δ 3.76 and 3.74) and with a relative ratio (estimated from the $^1H$ NMR integration) following that of the other coexisting two pairs of methyls at δ 3.03, 3.64 and 3.57, 3.68, which were also present in the starting material, suggested a rather similar structure for the components of the mixture in question. The chemical shifts of the new-entered methyls are representative for indole N-$CH_3$ substituents.[13a] Furthermore, the methylation product was ascertained to be coincident with the product **10b** (mixture of $\mathbf{10b_1}$ and $\mathbf{10b_2}$).

$$\mathbf{10a} \xrightarrow[DMF]{KOH\,/\,CH_3I} \mathbf{10b}$$

The formation of isoxazolidines **9** and **10** is regarded to follow a scheme including a successive process of nitrone **8** generation and its 1,3-dipolar cycloaddition reaction with methyl acrylate (Scheme 2). This point is supported by the fact that nitrones **8a** and **8b** were quantitatively (84% and 80% yield) isolated as precipitated solids from the reactions of **2b** and **2c** with **1a** respectively. They were characterized by the low field triplet (δ 4.11) and doublet of doublets (δ 5.38) respectively for the N(O)$CH_2$ and N(O)CHC=O protons as well as by the singlets at δ 8.18 and 8.50 respectively for the CH=N(O) protons. In both cases, a single stereoisomer, probably[18, 19a] the Z-, was detected by the $^1H$ NMR spectra. On further treatment with

refluxing methyl acrylate, nitrone **8a** afforded the N-substituted isoxazolidines **9c$_1$**, **9c$_2$** and **10c$_1$**, **10c$_2$** (relative ratio ~ 1.3 : 1) in high total yield (88%). From the reaction mixture, only the isoxazolidine **9c$_2$** was isolated in pure state. The rest of the products were characterized from their mixture. Nitrone **8b** proved to be more inactive than **8a** and recovered unchanged (in 75%) under similar reaction conditions. The reaction product was an extremely complicated mixture from which the isoxazolidines **9,10d** were detected and separated, although not in analytically pure state, after repeated column chromatography (with mixtures of light petroleum/ethyl acetate or dichloromethane/ethyl ether as the eluent) in about 4% total yield.




Scheme 3

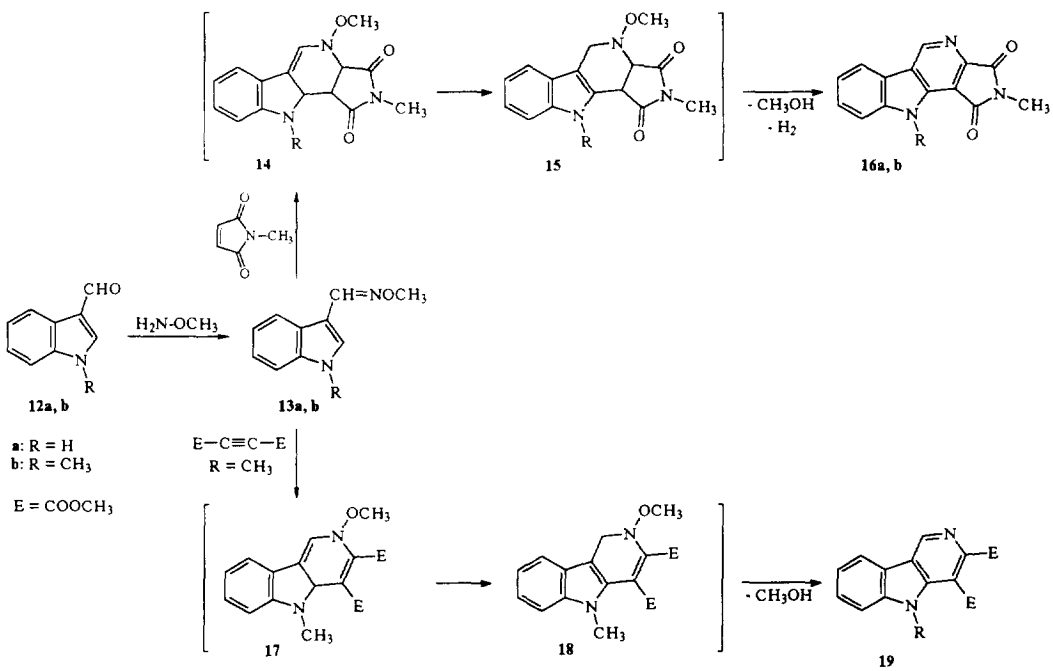
All of the reactions studied exhibited poor *regio* and *stereo*-selectivity, ranging from 1 : 1.3 - 1 : 1.4 and 1 : 1.1 - 1 : 2 respectively. It is worth to mention that from the reactions of **8a** and **8b** with methyl acrylate the isoxazolidines **9,10a** were also obtained in low total yields (4 - 10%) along with the products **9,10c** and **9,10d** respectively. Their formation is attributed to a fragmentation of the nitrones **8** to the corresponding oxime **1a** (Scheme 3, route 1) which has been reported[16, 19] to occur thermally or even at r.t. when the nitrone nitrogen bears an electron-withdrawing group. In the presence of methyl acrylate the oxime is converted to the isoxazolidines **9,10a** through an analogous with the above mentioned tandem process. A process involving generation of isoxazolidine **11** through an abstraction of the $R^1CH=CHCOR^2$ group from **9,10c,d** followed by a Michael addition of **11** to methyl acrylate (Scheme 3, route 2) could also be considered possible because in a control experiment the isoxazolidines **9,10a** were formed after prolonged refluxing of a mixture of **9,10c** (all the four isomers) in methyl acrylate although in essentially lower yield in respect with that observed in the reaction of the nitrone **8a** with methyl acrylate.

In the $^1$H NMR spectra of some fractions collected from the reaction mixture of **8b** with methyl acrylate, signals appear at field values [e.g. δ 5.71 (d), 5.37 (t) in one of them or 5.39 (dd), 5.73 (dd) or 6.40 (d), 5.29 (m), 4.33 (dd) in two others] lower than that expected for the cycloaddition products of aldonitrones with methyl acrylate (δ ~ 2.3 - 4.9).[13a, 17, 20] These signals could be attributed to the cycloaddition products of the N-methylmaleimide with the nitrone **8b** or with the non-isolated nitrone **8** ($R=R^1=H$, $R^2=OCH_3$). The latter nitrone, as well as N-methylmaleimide, could be assumed to derive through the fragmentation mode of

nitrone **8b** depicted in Scheme 3 (route 1). Unfortunately, the large number of the products obtained, accompanied by the low total yield as well as by the extreme difficulty to separate them by column chromatography resulted in our failure to isolate analytically pure samples in order to identify them completely.

The isoxazolidines **9** and **10** were proved sensitive to treament with acids. Efforts to convert them to fused[b]indole derivatives through acid induced (PPA) intramolecular acylation lead to decomposition products.

The failure of the oximes **1a,b** to afford Diels-Alder products with the electrophilic alkenes tested could be attributed to the conjugative effect of the indole nitrogen atom which may increase the nucleophilic capacity of the oxime nitrogen atom, thus enhancing its Michael donor behaviour towards the electron-deficient dipolarophile and therefore resulting to nitrone intermediates through the hydroxy hydrogen transfer. In order to exclude this potentiality (hydrogen transfer) we have substituted an O-Me group for the O-H of the oxime. In reality, the objective of an heterodiene behaviour was achieved with the O-Me oximes **13a,b**.




Scheme 4

The oximes **13a**[21] and **13b**[22] were prepared from the corresponding aldehydes **12a,b** and used as mixtures of E, Z isomers (in 1 : 1.6 and 1 : 1.1 ratio respectively) as indicated by their $^1$H NMR spectra. The reactions of the oxime **13b** with refluxing methyl acrylate or with N-methylmaleimide in refluxing benzene or toluene failed to proceed. So, the low boiling point methyl acrylate and methyl vinyl ketone were not

tested as possible dienophiles in the reactions attempted. Instead, N-methylmaleimide and dimethyl acetylenedicarboxylate (DMAD) were used. The reactions were performed in refluxing mesitylene and the alkene or the alkyne was used in slight excess with respect to the oxime (1.1 : 1 molar ratio).

From the reactions of **13a** and **13b** with N-methylmaleimide the fused γ-carbolines **16a** and **16b** (Scheme 4) were precipitated and isolated by filtration in 53 and 64% yield respectively. In contrast, the reactions of DMAD with the oximes **13a** and **13b** resulted in extremely complicated product mixtures which were subjected to chromatorgaphic separation. However, the isolation of the 1,2-disubstituted γ-carboline **19** from the latter reaction mixture was only succeeded, in 14% yield, whereas the corresponding product could not be detected at all in the former one.

The γ-carbolines **16** and **19** are obviously derived from a [4+2] cycloaddition reaction. The intermediates **14** and **17** (Scheme 4), which are supposed to be initially formed, are further transformed to **15** and **18** respectively, due to the indole ring aromatization making them more stable than their precursors. By elimination of methanol, which in the case of the intermediate **15** is accompanied by thermally induced dehydrogenation the partially saturated fused pyridine ring is aromatized affording the more stable γ-carbolines **16** and **19**. Similar procedures have been referred[5, 11] for analogous systems.

The molecular ion peak in the mass spectrum of product **19** confirms the abstraction of methanol from the 1 : 1 product, whereas the mass spectra of **16a,b** demonstrate the abstraction of one molecule of hydrogen in addition. Products **16a,b** and **19** were mainly recognized by their characteristic $^1$H NMR spectra, which are in accordance with data reported in literature.[11] Namely, singlets for the $CON(CH_3)CO$ group appear at δ 3.11 and 3.10 in the spectra of **16a** and **16b** respectively whereas one more singlet at δ 4.39 for the $N\text{-}CH_3$ (aromatic) appears in the spectrum of the latter. Three singlets at δ 4.06, 3.99 and 3.97 in the spectrum of **19** are indicative for the presence of one $N\text{-}CH_3$ (aromatic) and two $COOCH_3$ groups. The deshielding of the aromatic $N\text{-}CH_3$ protons of **16b** with respect to the corresponding protons of **19** is probably attributed to the deshielding effect of the fixed dicarboximido group. The 1-methoxycarbonyl group of **19** is more flexible and causes smaller deshielding effects. The presence of the fused pyridine ring in products **16a, 16b** and **19** becomes evident by the singlets at δ 9.66, 9.63 and 8.89 respectively.

In conclusion, the nucleophilic O-H indolyl-oximes **1a,b** are not good 1-aza-1,3-butadienes for the electron deficient dipolarophiles tested, perhaps due to the possibility of the NOH hydrogen transfer. Instead, they readily afford the nitrones **8**, which can either be isolated or further react with the dipolarophiles to furnish the indolyl-isoxazolidines **9** and **10**. The exclusion of such a hydrogen transfer in the $N\text{-}OCH_3$ indolyl-oximes **13a,b** prevents their transformation to nitrones and permits their 4π-participation in Diels-Alder reactions with electron deficient dienophiles, thus providing a short, efficient and promising route to substituted or fused γ-carbolines.

## EXPERIMENTAL

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 297 spectrometer. $^1$H NMR spectra were recorded on a Bruker 300 AM spectrometer at 300 MHz and $^{13}$C NMR spectra on the same spectrometer at 75.5 MHz, in deuteriochloroform solutions, unless otherwise specified and are quoted relative to tetramethylsilane as

internal reference. Mass spectral data were obtained from a VG TS-250 Model instrument operating at 70 eV. Microanalyses were performed with a Perkin-Elmer Model 240B analyser. Column chromatography was performed over Merck Kieselgel (particle size 0.063-0.200 mm). Light petroleum refers to the fraction 40-60 °C.

*Preparation of the Starting Materials.* Indol-3-yl-carbaldehyde oxime,[14] 1-methylindol-3-yl-carbaldehyde oxime,[15] indol-3-yl-carbaldehyde O-methyl oxime[21] and 1-methylindol-3-yl-carbaldehyde O-methyl oxime[22] were prepared acording to literature methods.

*General Procedure for the Reactions of the Oximes **1, 13** or the Nitrones **8** with the Electrophilic Alkenes **2** or DMAD.* A mixture of the oxime **1** or **13** or the nitrone **8** with the alkene **2** or with DMAD in benzene (for the oximes **1**) or mesitylene (for the oximes **13**) was refluxed until no progress of the reaction was indicated by TLC (15 h - 5 d). The molar ratio of the oxime to the alkene/alkyne used was 1 : 1.1 in the case of the oximes **13a,b** and 1 : 2.2 in the case of the oximes **1a,b** with the exception of methyl acrylate which in the reactions with the oximes **1** or with the nitrones **8** was used in great excess in the absence of any other solvent. In the case of the reactions of the oxime **1a** with the alkenes **2b** or **2c** as well as of the oximes **13a** and **13b** with **2c** the products **8a**, **8b**, **16a** and **16b** respectively were precipitated in the reaction mixture and were isolated by filtration. Due to their insolubility they were purified by exhaustive washing with $CH_2Cl_2$, $Et_2O$, $CH_3COOCH_2CH_3$ and EtOH only. In all other cases the solvent was evaporated in *vacuo* and the residue was subjected to column chromatography using mixtures of light petroleum / ethyl acetate (3 : 1 - 1 : 1) as the eluent.

*Reaction of **1a** with **2a**.* From the column chromatography (eluent light petroleum / ethyl acetate 2 : 1) there were obtained in order of elution: (a) 43 mg mixture of **10a**$_1$, **10a**$_2$ in relative ratio 1.25 : 1 (NMR integration), (b) 90 mg mixture of **9a**$_1$, **9a**$_2$, **10a**$_1$ and **10a**$_2$ in relative ratio 5 : 1 : 9.7 : 5.2 (NMR integration), (c) 115 mg mixture of **9a**$_1$ and **9a**$_2$, **10a**$_1$ and **10a**$_2$ in relative ratio ~ 1.7 : 4.9 : 2 : 1 and (d) 81 mg mixture of **9a**$_1$ and **9a**$_2$ in relative ratio 1 : 2.8 (NMR integration). After repeated column chromatographies the fraction (d) was separated to its components **9a**$_1$ and **9a**$_2$. Separation of the compounds **10a**$_1$ and **10a**$_2$ from fraction (a) was unsuccessful. Mixture of the stereoisomers *(3R*,4S*)-* and *(3R*,4R*)-3-(indol-3-yl)-4-methoxycarbonyl-2-(2-methoxycarbonylethyl)isoxazolidines* **10a**$_1$ and **10a**$_2$ : oil, total yields 27 and 16% respectively; IR (neat) $cm^{-1}$ : 3380 (NH), 1730 (CO); $^1H$ NMR δ: 2.47-2.80 (m), 2.80-3.07 (m, hidden), 3.01 (s), 3.17 (broad), 3.56 (s), 3.61 (s), 3.67 (s), 3.48-3.71 (m, hidden), 3.71-3.94 (m), 4.14-4.60 (m), 6.96-7.23 (m), 7.32 (t, J=8.5 Hz), 7.64 (d, J=7.7 Hz), 7.74 (d, J=7.8 Hz), 8.72 (br s); $^{13}C$ NMR δ: 33.0, 33.1, 51.2, 51.4, 51.5, 51.8, 52.1, 52.2 (broad), 52.7, 54.8 (broad), 66.0 (broad), 67.5 (broad), 67.7 (broad), 68.4, 111.1, 111.4, 111.7, 118.9, 119.3, 119.5, 119.6, 121.8, 122.2, 123.3, 123.4, 125.8, 126.5, 135.8, 136.6, 171.4, 172.7, 173.2; MS m/z: 332 ($M^+$, 33), 301 (4), 246 (20), 214 (48), 170 (12), 154 (22), 130 (14), 84 (100), 55 (82); Anal. Calcd. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.30; H, 5.92; N, 8.28%. *(3R*,5S*)-3-(indol-3-yl)-5-methoxycarbonyl-2-(2-methoxycarbonylethyl)isoxazolidine* **9a**$_1$: oil, total yield 19%; IR (neat) $cm^{-1}$ : 3380 (NH), 1730 (CO); $^1H$ NMR δ: 2.60-2.76 (m, 2H), 2.76-2.87 (m, 1H), 2.87-3.13 (m, 2H), 3.18 (broad, 1H), 3.59 (s, 3H), 3.81 (s, 3H), 4.05 (broad, 1H), 4.69 (dd, 1H, J=9.2, 5.9 Hz), 7.11 (t, 1H, J=7.35 Hz), 7.20 (s, 1H), 7.21 (t, 1H, J=7.4

Hz), 7.37 (d, 1H, J=7.7 Hz), 7.68 (d, 1H, J=7.8 Hz), 8.17 (br s, 1H); $^{13}$C NMR δ: 33.2, 40.6 (broad), 51.5, 52.3, 52.35 (broad), 63.8 (broad), 74.3 (broad), 111.27, 111.34, 119.7, 119.8, 122.4, 122.5, 122.9, 136.3, 172.8, 172.9; MS m/z: 332 ($M^+$, 10), 301 (6), 246 (18), 214 (100), 154 (56), 130 (38), 89 (26), 55 (36); Anal. Calcd. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.30; H, 6.01; N, 8.35%. *(3R*,5R*)-3-(indol-3-yl)-5-methoxycarbonyl-2-(2-methoxycarbonylethyl)isoxazolidine* **9a$_2$**: oil, total yield 38%; IR (neat) cm$^{-1}$ : 3375 (NH), 1735 (CO); $^1$H NMR (25 °C) δ: 2.69 (t, 2H, J=6.9 Hz), 2.73-2.82 and 2.82-2.96 (two overlapped m, 2H), 3.17 and 3.21 (two broads, 2H), 3.56 (s, 3H), 3.79 (s, 3H), 4.22 (broad, 1H), 4.76 (dd, 1H, J=9.1, 5.3 Hz), 7.10 (overlapped s and t, 2H, J=7.35 Hz), 7.18 (t, 1H, J=7.45 Hz), 7.34 (d, 1H, J=7.9 Hz), 7.69 (d, 1H, J=7.7Hz), 8.73 (br s, 1H). Peaks at δ 3.17, 3.21 and 4.22 become two multiplets and a triplet (J=7.6 Hz) when the spectrum is recorded at 50 °C ; $^{13}$C NMR (50 °C) δ: 33.1, 40.5 51.3, 52.0 (broad), 52.1, 63.0, 75.1, 111.4, 112.3, 119.3, 119.5, 122.2, 122.3, 126.1, 136.7, 172.1, 172.7. When the spectrum was recorded at 25 °C, the signals at δ 40.5 and 63.0 appeared as broads; MS m/z: 332 ($M^+$, 66), 301 (5), 246 (27), 214 (100), 154 (25), 130 (31), 89 (9), 55 (28); Anal. Calcd. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.49; H, 6.12; N, 8.40%.

*Reaction of* ***1b*** *with* ***2a***. There were obtained in order of elution (eluent light petroleum / ethyl acetate 2 : 1) : (a) 96 mg mixture of **9b$_1$**, **10b$_1$** and **10b$_2$** in relative ratio ~ 1 : 3.5 : 4 (NMR integration), (b) 147 mg mixture of **9b$_1$**, **9b$_2$**, **10b$_1$** and **10b$_2$** in relative ratio ~ 3.5 : 3.8 : 1.7 : 1 (NMR integration) and (c) 59 mg of compound **9b$_2$**. A mixture of **10b$_1$** and **10b$_2$** was separated from the fraction (a) but the compound **9b$_1$** was not separable and was characterized from its mixture. Mixture of the diastereoisomers *(3R*,4S*)-* and *(3R*,4R*)-3-(1-methylindol-3-yl)-4-methoxycarbonyl-2-(2-methoxycarbonylethyl)isoxazolidines* **10b$_1$** and **10b$_2$** : oil, total yields 19 and 17% respectively; IR (neat) cm$^{-1}$ : 1730 (CO); $^1$H NMR δ: 2.56-2.75 (m), 2.84-3.02 (m), 3.03 (s), 3.02-3.23 (broad), 3.57 (s), 3.64 (s), 3.68 (s), 3.74 (s), 3.76 (s), 3.57-3.88 (m, hidden), 4.19-4.35 (m), 4.42 (t, J=8.1 Hz), 7.05-7.16 (m), 7.16-7.34 (m), 7.62 (d, J=8.9 Hz), 7.73 (d, J=8.0 Hz); $^{13}$C NMR δ: 32.76, 32.8, 33.1, 33.2, 51.2, 51.4, 51.5, 52.1, 52.7, 55.1 (broad), 67.5 (broad), 68.4 109.1, 109.3, 109.4, 110.6 (broad), 119.1, 119.16, 119.25, 119.9, 121.6, 121.9, 126.4, 127.7, 127.9, 137.4, 171.3, 172.6, 173.7, 173.1; MS m/z: 346 ($M^+$, 64), 260 (53), 228 (100); Anal. Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.30; H, 6.28; N, 7.88%. *(3R*,5S*)-3-(1-methylindol-3-yl)-5-methoxycarbonyl-2-(2-methoxycarbonylethyl)isoxazolidine* **9b$_1$**: total yield 18%; $^1$H NMR δ: 2.62-2.90 (two overlapped m, 3H), 2.90-3.08 (m, 3H), 3.19 (broad, 1H), 3.63 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 4.04 (broad, 1H), 4.67 (dd, 1H, J=9.3, 5.6 Hz), 7.11 (s, 1H), 7.14 (t, 1H, J=7.1 Hz), 7.20-7.42 (m, 2H), 7.69 (d, 1H, J=7.9 Hz). *(3R*5R*)-3-(1-methylindol-3-yl)-5-methoxycarbonyl-2-(2-methoxycarbonylethyl)isoxazolidine* **9b$_2$**: oil, total yield 33%; IR (neat) cm$^{-1}$ : 1730 (CO); $^1$H NMR δ: 2.59-2.95 (m, 4H), 3.03 (broad, 1H), 3.18 (broad, 1H), 3.59 (s, 3H), 3.76(s, 3H), 3.80 (s, 3H), 4.23 (broad, 1H), 4.74 (dd, 1H, J=8.8, 5.2 Hz), 7.07 (s, 1H), 7.12 (t, 1H, J=7.3 Hz), 7.17-7.37 (m, 2H), 7.69 (d, 1H, J=7.7 Hz); $^{13}$C NMR δ: 32.7, 33.2, 41.0, 51.4, 52.2 (broad), 52.3, 63.0 (broad), 75.0, 109.4, 110.9, 119.3, 119.6, 121.9, 126.5, 127.1, 137.3, 172.1, 172.7; MS m/z: 346 ($M^+$, 64), 260 (12), 228 (100); Anal. Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.35; H, 6.37; N, 7.85%.

*Reaction of* ***1a*** *with* ***2b***. *C-(Indol-3-yl)-N-(2-oxo-but-4-yl)-nitrone* **8a** was precipitated. Yield 84% (192 mg), m.p. 186-188 °C; IR (nujol) cm$^{-1}$: 3120 (NH), 1690 (CO), 1595 (C=N), 1150 (N→O); $^1$H NMR (DMSO-d$_6$) δ: 2.10 (s, 3H), 2.99 (t, 2H, J=6.5 Hz), 4.11 (t, 2H, J=6.5 Hz), 7.07 (t, 1H, J=7.7 Hz), 7.14 (t, 1H, J=7.8 Hz), 7.41 (d, 1H, J=7.8 Hz), 7.76 (d, 1H, J=7.6 Hz), 8.18 (s, 1H), 8.75 (d, 1H, J=2.3 Hz), 11.57 (br s, 1H); $^{13}$C NMR (DMSO-d$_6$) δ:

29.8, 40.4, 58.4, 107.2, 111.9, 118.1, 119.9, 122.2, 125.7, 127.5, 128.2, 135.4, 206.3; MS m/z: 230 ($M^+$, 100), 187 (7), 173 (16), 160 (30), 144 (25), 117 (47), 89 (14), 55 (11); Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.68; H, 6.02; N, 11.88%.

*Reaction of* ***1a*** *with* ***2c****.* *C-(Indol-3-yl)-N-(2,5-dioxo-1-methylpyrrol-3-yl)-nitrone* **8b** was precipitated. Yield 80% (217 mg), m.p. 223-224 °C (dec); IR (nujol) $cm^{-1}$: 3120 (NH), 1720, 1700 (CO) ; $^1H$ NMR (DMSO-$d_6$) δ: 2.90 (s, 3H), 3.01-3.22 (m, 2H), 5.38 (dd, 1H, J=7.9, 4.0 Hz), 6.99-7.27 (m, 2H), 7.41 (d, 1H, J=7.5 Hz), 7.84 (d, 1H, J=7.3 Hz), 8.50 (s, 1H), 8.78 (d, 1H, J=2.5 Hz), 11.73 (br s, 1H); $^{13}C$ NMR (DMSO-$d_6$) δ: 24.8, 32.8, 69.3, 106.7, 112.1, 118.1, 120.3, 122.5, 125.8, 129.3, 130.4, 135.5, 173.0, 175.3; MS m/z: 271 ($M^+$, 43), 160 (79), 142 (49), 117 (100), 89 (35), 54 (46); Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 62.20; H , 4.91; N, 15.65%.

*Reaction of* ***8a*** *with* ***2a****.* There were obtained in order of elution (light petroleum / ethyl acetate 3 : 2): (a) 33 mg mixture of $\mathbf{9a_1}$, $\mathbf{9a_2}$, $\mathbf{10a_1}$ and $\mathbf{10a_2}$, (b) 133 mg mixture of $\mathbf{9c_1}$, $\mathbf{10c_1}$ and $\mathbf{10c_2}$ in relative ratio ~ 1.8 : 1 : 1.5 (NMR integration), (c) 91 mg mixture of $\mathbf{9c_1}$, $\mathbf{9c_2}$, $\mathbf{10c_1}$ and $\mathbf{10c_2}$ in relative ratio ~1.7 : 1.1 : 1.6 : 1 (NMR integration) and (d) 54 mg of $\mathbf{9c_2}$. The chromatographic separation of compounds $\mathbf{9c_1}$, $\mathbf{10c_1}$ and $\mathbf{10c_2}$ was not attainable. Mixture of the stereoisomers *(3R*,4S*)-* and *(3R*,4R*)-3-(indol-3-yl)-4-methoxycarbonyl-2-(2-oxo-but-4-yl)isoxazolidines* $\mathbf{10c_1}$ and $\mathbf{10c_2}$ with the regioisomer *(3R*,5S*)-3-(indol-3-yl)-5-methoxycarbonyl-2-(2-oxo-but-4-yl)isoxazolidine* $\mathbf{9c_1}$: oil, total yields 18, 20 and 27% respectively ; IR (neat) $cm^{-1}$ : 1735, 1710 (CO); $^1H$ NMR δ: 2.02 (s), 2.04 (s), 2.07 (s), 2.62-2.96 (m), 2.99 (s), 3.12 (broad), 3.63 (s), 3.78 (s), 3.61-3.88 (two overlapped m), 4.43 (t, J=7.9 Hz), 4.68 (dd, J=9.1, 5.1 Hz), 6.98-7.20 (m), 7.25-7.36 (m), 7.64 (two overlapped m), 7.72 (d, J=7.7 Hz), 9.09 and 9.13 (two br s); $^{13}C$ NMR δ: 29.9, 30.07, 30.14, 40.2 (broad), 41.58, 41.61, 41.8, 51.0, 51.94, 51.97, 52.4, 63.9 (broad), 66.0 (broad), 67.3, 67.7 (broad), 68.2, 74.8 (broad), 111.1, 111.36, 111.44, 118.7, 119.1, 119.2, 119.3, 121.6, 121.8, 121.9, 123.2, 123.4, 123.5, 125.6, 125.7, 126.3, 135.7, 136.4, 136.5, 171.4, 173.0, 173.1, 208.0, 208.2, 208.7; MS m/z: 316 ($M^+$, 49), 230 (21), 214 (100), 154 (28), 130 (11); Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.31; H, 6.21; N, 8.60%. *(3R*,5R*)-3-(indol-3-yl)-5-methoxycarbonyl-2-(2-oxo-but-4-yl)isoxazolidine* $\mathbf{9c_2}$ : oil, total yield 23%; IR (neat) $cm^{-1}$ : 3380 (NH), 1730, 1700 (CO); $^1H$ NMR δ: 2.06 (s, 3H), 2.69-2.94 (m, 4H), 3.01 and 3.20 (two broads, 2H), 3.79 (s, 3H), 4.20 (broad, 1H), 4.75 (dd, 1H, J=9.3, 5.3 Hz), 7.10 (t and hidden s, 2H, J=7.4 Hz), 7.18 (t, 1H, J=7.6 Hz), 7.34 (d, 1H, J=8.1 Hz), 7.69 (d, 1H, J=7.8 Hz), 8.81 (br s, 1H); $^{13}C$ NMR δ: 30.1, 40.7 (broad), 42.0, 51.6 (broad), 52.3, 63.2 (broad), 74.9, 111.4, 111.8, 119.2, 119.5, 122.1, 122.8, 125.9, 136.5, 172.1, 208.2. MS m/z: 316 ($M^+$, 24), 230 (8), 214 (100), 154 (33), 130 (21), 89 (7), 55 (14); Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.31; H, 6.21; N, 8.68%.

*Reaction of* ***13a*** *with* ***2c****.* The insoluble *3,4-(N-methyl-dicarboximido)-γ-carboline* **16a** was precipitated in 45% yield (112 mg). After evaporation of the solvent in *vacuo* and trituration of the residue with dichloromethane and ethyl ether a second crop of **16a** was collected (48 mg, 19%, total yield 64%), m.p. >320 °C; IR (nujol) $cm^{-1}$: 3140 (NH), 1760, 1705 (CO); $^1H$ NMR (DMSO-$d_6$) δ: 3.10 (s, 3H), 7.38 (t, 1H, J=7.4 Hz), 7.59 (t, 1H, J=7.5 Hz), 7.68 (d, 1H, J=7.8 Hz), 8.37 (d, 1H, J=8.0 Hz), 9.63 (s, 1H), 12.71 (br s, 1H); $^{13}C$ NMR: a good quality spectrum was not achievable, due to the insolubility of **16a** even in DMSO; MS m/z: 251 ($M^+$, 57), 194 (21), 168 (30), 57 (100); Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.61; N, 16.72. Found: C, 66.65; H, 3.50; N, 16.60%.

*Reaction of **13b** with **2c**.* The insoluble *3,4-(N-methyl-dicarboximido)-5-methyl-γ-carboline* **16b** was isolated by filtration (59 mg, 22%). A second crop of **16b** was precipitated and collected by filtration (82 mg, 31%, total yield 53%) after concentration of the initial filtrate and trituration of the residue with dichloromethane. M.p. 316-318 °C; IR (nujol) $cm^{-1}$: 1755, 1695 (CO); $^1H$ NMR (DMSO-$d_6$) δ: 3.11 (s, 3H), 4.39 (s, 3H), 7.46 (t, 1H, J=7.2 Hz), 7.69 (t, 1H, J=7.25 Hz), 7.78 (d, 1H, J=7.6 Hz), 8.42 (d, 1H, J=7.5 Hz), 9.66 (s, 1H); $^{13}C$ NMR: a good quality spectrum was not attainable, due to the insolubility of compound **16b** even in DMSO; MS m/z: 265 ($M^+$, 100), 208 (14), 182 (37), 57 (17); Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 68.02; H, 4.26; N, 16.00%.

*Reaction of **13b** with DMAD. 3,4-Bis-methoxycarbonyl-5-methyl-γ-carboline* **19** was obtained from the column chromatography (eluent light petroleum/ethyl acetate 2 : 1) and was further purified by column chromatography with dichloromethane/light petroleum 10 : 1 as the eluent. Yield 14% (47 mg), m.p. 176-177 °C (from dichloromethane-ethyl ether); IR (nujol) $cm^{-1}$: 1745, 1710 (CO); $^1H$ NMR δ: 3.97 (s, 3H), 3.99 (s, 3H), 4.06 (s, 3H), 7.38 (t, 1H, J=7.15 Hz), 7.50 (d, 1H, J=7.7 Hz), 7.62 (t, 1H, J=7.25 Hz), 8.12 (d, 1H, J=7.5 Hz), 8.89 (s, 1H); $^{13}C$ NMR δ: 28.1, 52.5, 53.0, 109.8, 115.6, 116.2, 120.0, 121.2, 121.6, 128.1, 130.1, 141.5, 149.5, 151.9, 166.2, 168.2; MS m/z: 298 ($M^+$, 100), 267 (52), 239 (47), 209 (18), 182 (29); Anal. calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.30; H, 4.60; N, 9.21%.

*Methylation of the Mixture of Isoxazolidines **10a**$_1$ and **10a**$_2$.* To a solution of the mixture of isoxazolidines (50 mg, 0.15 mmol) in DMF (3 ml), potassium hydroxide (25 mg) and methyl iodide (0.03 ml) were added and the mixture was stirred at room temperature for 3 h. Water was added and the mixture was extracted with dichloromethane. The organic layer was dried over sodium sulfate and after evaporation of the solvent the residue was subjected to column chromatography (eluent light petroleum/ethyl acetate 2 :1) to afford the mixture of the diastereoisomers **10b**$_1$ and **10b**$_2$ in 80% yield (40 mg).

## REFERENCES


1. (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, San Diego, 1987; (b) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, 113, 1713 ; (c) Boger, D. L. *Tetrahedron* **1983**, 39, 2869.
2. (a) Cheng, Y.-S.; Lupo, Jr., A.-T.; Fowler, F. W. *ibid.* **1983**, 105, 7696; (b) Hwang, Y. C.; Fowler, F. W. *J. Org. Chem.* **1985**, 50, 2719 and references cited therein; (c) Teng, M.; Fowler, F. W. *ibid.* **1990**, 55, 5646; (d) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, 111, 1517; (e) Boger, D. L.; Corbett, W. L.; Wiggins, J. M. *J. Org. Chem.* **1990**, 55, 2999; (f) Boger, D. L.; Curran, T. T. *ibid.* **1990**, 55, 5439.
3. (a) Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, 23, 3261; (b) Tamura, Y.; Tsugoshi, T.; Nakajima, Y.; Kita, Y. *Synthesis*, **1984**, 930; (c) Dolle, R. E.; Armstrong, P. W.; Shaw, A. N.; Novelli, R. *Tetrahedron Lett.* **1988**, 29, 6349; (d) Waldner, A.; *Helv. Chim. Acta* **1989**, 72, 1435; (e) Potts, K. T.; Walsh, E. B.; Bhattacharjee, D. *J. Org. Chem.* **1987**, 52, 2285; (f) Chigr, M.; Fillion, H.; Rougny, A. *Tetrahedron Lett.* **1988**, 29, 5913; (g) Allcock, S. J.; Gilchrist, T. L.; Shuttleworth, S. J. *Tetrahedron* **1991**, 47, 10053.
4. Kusurkar, R. S.; Bhosale, D. K. *Tetrahedron Lett.* **1991**, 32, 3199.
5. Boger, D. L.; Zhu, Y. *Tetrahedron Lett.* **1991**, 32, 7643.

6. Armstrong, P.; Grigg, R.; Warnock, W. J. *J. Chem. Soc., Chem. Comm.* **1987**, 1325.
7. Grigg, R.; Heaney, F.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron*, **1991**, 47, 4007.
8. Grigg, R.; Perrior, T. R.; Sexton, G. J.; Surendrakumar, S.; Suzuki, T. *J. Chem. Soc., Chem. Comm.* **1993**, 372.
9. Bishop, R.; Brooks, P. R.; Hawkins, S. C. *Synthesis* **1988**, 997.
10. (a) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, 48, 6929; (b) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, 47, 10339.
11. Biswas, G. K.; Nath, A. C.; Mukherjee, B.; Patra, A.; Chakrabarty, M. *Tetrahedron Lett.* **1992**, 33, 117.
12. Shimoji, Y.; Hashimoto, T.; Furukawa, Y.; Yanagisawa, H. *Heterocycles* **1993**, 36, 123.
13. (a) Malamidou-Xenikaki, E.; Stampelos, X. N.; Coutouli-Argyropoulou, E.; Cardin, C. J.; Teixeira, S.; Kavounis, C. A. *J. Chem. Soc., Perkin Trans. 1*, 000; (b) Malamidou-Xenikaki, E.; Coutouli-Argyropoulou E. *Liebigs Ann. Chem.* **1992**, 75; (c) Coutouli-Argyropoulou E.; Malamidou-Xenikaki, E. *J. Heterocyclic Chem.* **1990**, 27, 1185.
14. Devys, M.; Barbier, M. *Synthesis* **1990**, 214.
15. Gower, B. G.; Leete E. *J. Am. Chem. Soc.* **1963**, 85, 3683.
16. Grigg, R.; Jordan, M.; Tangthongkum, A.; Einstein, F.W.B.; Jones, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 47.
17. (a) Ali, Sk. A.; Almuallen, H. A. *Tetrahedron* **1992**, 48, 5273; (b) Aurich, H. G.; Frenzen, G.; Rohr, M. G. *Tetrahedron* **1994**, 50, 7417.
18. Padwa, A.; Fisera, L.; Kochler, K. F.; Rondriguez, A.; Wong, G. S. K. *J. Org. Chem.* **1984**, 49, 276.
19. (a) Kim, H. K.; Weintraub, P. M. *J. Org. Chem.* **1970**, 35, 4282; (b) Goodrow, M. H.; Villarreal, J. A.; Grubbs, E. J. *ibid.* **1974**, 39, 3447; (c) Boyd, D. R.; Neill, D. C. *J. Chem. Soc., Perkin 1* **1977**, 1308; (d) Boyd, D. R.; Neill, D. C.; Stubbs, M.E. *J. Chem. Soc., Perkin 2* **1978**, 30.
20. Grünanger, P. ; Vita-Fintzi, P. *"The Chemistry of Heterocyclic Compounds"*, vol. 49, part 1, Taylor, E. C.; Weissberger, A. Eds., Wiley, N. York, **1991**, p. 659.
21. Kostyuchenko N. P.; Zhirnova, K. G.; Preobrazhenskaya, M. N.; Sheinker, Yu. N.; Suvorov, M. N. ; *J. Org. Chem. USSR*, **1972**, 8, 2469; *Chem. Abstr.* **1973**, 78, 110408g.
22. Feuer, H.; Braunstein, D. M. *J. Org. Chem.* **1969**, 34, 1817.

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