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Esters of Feist's Acid: Some Insights into the Electronic Structure and Reactivity of Methylenecyclopropanes Ring-Substituted with Acceptor Groups

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Dedicated to Professor Dr. R. R. Kostikov on the occasion of his 70th birthday

Keywords: Cycloaddition / Electronic structure / Methylenecyclopropane / Nitrone / Substituent effects

1,3-Dipolar cycloaddition of *C*-aryl-*N*-aryl- or *N*-methylnitrones with esters of Feist's acid (3-methylenecyclopropane-*trans*-1,2-dicarboxylic acid) occurs with the formation of the corresponding spiro[cyclopropane-1,4-isoxazolidine] cycloadducts as single isomer with yields in the range of 17–59 %. The reaction proceeds with inverse regiochemical outcome compared to cycloadditions with unsubstituted methylenecyclopropane. Feist's esters are significantly less active towards cycloaddition with nitrones than methylenecyclopropane and reactions require prolonged heating at elevated temperature. The electronic structures of Feist's esters were investigated by means of molecular photoelectron spectroscopy and theoretical calculations (HF/6-31G*, B3LYP/6-31G*). Both, measured photoelectron He^{I} spectrum and ground state calculations (HF/6-31G*) of Feist's esters, indicate considerable lowering of the methylenecyclopropane π-HOMO energies by substitution with an acceptor group. B3LYP calculations of addends and transition states for the interaction of methylenecyclopropane with *C*,*N*-diphenylnitrone correctly predict regiochemical outcome. However, B3LYP calculations do not account for the observed regiochemical outcome and diminished reactivity in reactions of Feist's esters with *C*,*N*-diphenylnitrone.

Introduction

Methylenecyclopropanes (MCPs) represent a valuable class of compounds for application in organic synthesis.[1] MCPs possess both high ring and double bond strain due to the presence of the three-membered ring.[1,2] The release of strain upon different types of addition or cycloaddition enhances reactivity of MCPs in comparison to unstrained hydrocarbons.[1,2] The cyclopropyl group is considerably smaller than an isopropyl group, allowing sterically sensitive reactions to proceed.[2d] At the same time the cyclopropyl group is a better donor for electron-deficient centers than simple dialkyl groups.[2d] The ability of cyclopropane ring to interact with different conjugated systems is remarkable.[2] For an acceptor-substituted cyclopropane ring, Hoffmann proposed an interaction between one of the occupied Walsh orbitals of the cyclopropane ring and the π* orbital of the electron-withdrawing substituent.[3] This interaction causes a transfer of electron density from the ring to the substituent. Thus, an important question arises to what extent can the reactivity of the C=C bond of MCPs be affected by the substitution of the three-membered ring? Our previous study of closely related substituted cyclopropenes reveals the great influence of substituents at the cyclopropane ring on the reactivity of cyclopropene C=C bonds in 1,3-dipolar cycloadditions with dipoles like carbonyl ylides and nitrones.[4] For example, the most sensitive reaction towards the substitution at the three-membered ring is cycloaddition of carbonyl ylides to 1,2-diphenylcyclopropenes. The corresponding cycloadducts were formed in yields of up to 92% with normal cyclopropenes, such as the unsubstituted parent 1,2-diphenylcyclopropene and its methylmonosubstituted derivative, but no reaction was observed or the yields of adducts were less than 5% in the case of ring-acceptor-substituted cyclopropenes.[4b,4c] Both, measured photoelectron spectra and ground state calculations of acceptor-substituted cyclopropenes, indicate considerable lowering of the HOMO energy (cyclopropene $\pi_{C=C}$ bond).[4b,5] Considering the vast number of publications on experimental properties and theoretical calculations of methylenecyclopropane (MCP) and its alkyl derivatives it is surprising that there are only few reports discussing MCPs with acceptor substituents at the three-membered ring.[1]

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The crystal structure data of methylenecyclopropane-2-carboxamide surprisingly show an angle distortion of the exocyclic methylene group.[6]

Intriguing examples of ring-acceptor-substituted MCPs are Feist's acid (3-methylenecyclopropane-*trans*-1,2-dicarboxylic acid) and the esters thereof – the first known derivatives of MCPs since 1893 (Figure 1).[7] Since that time Feist's acid and esters have been a subject of much research including preparation of Feist's acid in enantiomeric form.[8] Some abnormalities in the properties of Feist's ester have been reported in comparison to parent MCP. First of all, the methylenecyclopropane system in Feist's acid and its esters shows remarkable thermal stability and resistance to alkaline degradation.[9] Feist's acid is completely inert towards the reaction with singlet oxygen whereas MCP and its alkyl derivatives yield a variety of products.[10] Also, in contrast to other MCPs derivatives Feist's acid dimethyl ester does not undergo peracid oxidation.[11] An anomalous frequency shift was observed for hydrogen out-of-plane deformations of the methylene group in IR spectra of Feist's acid derivatives ($\nu_{C=CH2}$ = 10.8–11.1 μ) as compared to parent MCP and unconjugated olefins ($\nu_{C=CH2}$ is about 11.25 μ).[12] 1,3-Dipolar cycloaddition of phenyl azide to dimethyl ester of Feist's acid leads to formation of 1-phenyl-4-[1,2-bis(methoxycarbonyl)ethyl]-1,2,3-triazole as consequence of the unusual rearrangement of an intermediate triazoline cycloadduct.[13] Previously, we reported on the first study of the 1,3-dipolar cycloaddition of carbonyl ylides to different MCPs.[14] Carbonyl ylide **3**, generated from the diazocarbonyl precursor **2** by dirhodium tetraacetate catalyzed decomposition, yields a diastereomeric mixture of isomers **5** with ring-substituted methylenecyclopropane **4** in 42% yield (Scheme 1). In contrast, no cycloadducts were formed from the attempted reaction with diethyl ester of Feist's acid **1b**. The latter was recovered from the reaction mixtures.

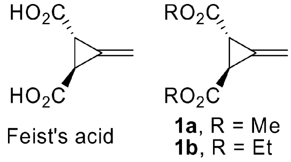
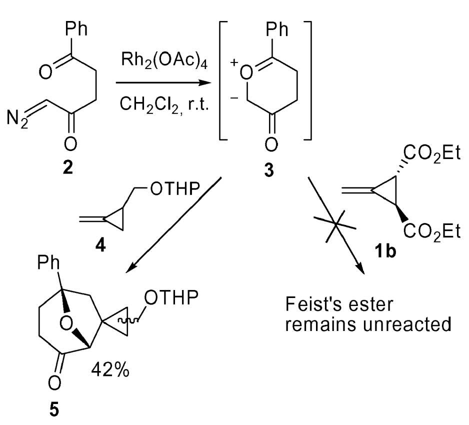


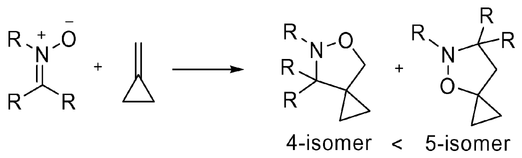
Figure 1. Structures of Feist's acid and its esters.



Scheme 1. Cycloadditions between the carbonyl ylide **3** and methylenecyclopropanes.

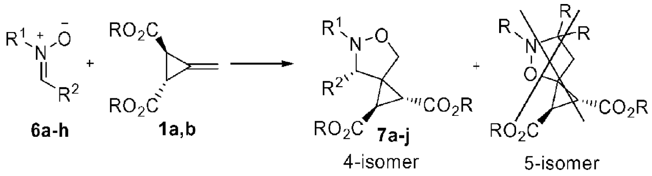
Results and Discussion

We decided to further investigate the reactivity of Feist's esters and their electronic structure. In this communication we discuss 1,3-dipolar cycloadditions of esters of Feist's acid with nitrones. In general, the 1,3-dipolar cycloaddition of nitrones to the C=C bond of MCPs is one of the most extensively studied reactions of this class due to the rich chemistry of cycloadducts with spirocyclopropyl moiety formed in the reactions.[1b,1e] In most cases spiro[cyclopropane-1,5-isoxazolidine] regioisomers are formed predominantly or even exclusively (Scheme 2).[1e] The driving force of the observed regioselectivity is considered to be the steric strain of the bulky nitrone dipole.[1e] As an example, *C*-phenyl-*N*-methylnitrone **6a** interacts with MCP with the formation of both spiro[cyclopropane-1,4(5)-isoxazolidines] in a ratio of 30:70 in favour of the 5-regioisomer.[15] The formation of 4-substituted isomeric isoxazolidines, however, is very common for the reactions of 1,1-disubstituted open-chain alkenes.[16]



Scheme 2. Regioselectivity in reactions of methylenecyclopropane with nitrones.

N-Methyl- and *N*-phenyl-*C*-arylnitrones **6** previously employed for cycloaddition with MCPs were selected as reference 1,3-dipole compounds for our study. In contrast to the reported reactions with parent unsubstituted MCP, nitrones **6** do not interact with Feist's esters at room temperature. However, monitoring of the reaction mixture of **6c** with the methyl ester **1a** of Feist's acid by means of ^{1}H NMR spectroscopy upon heating a benzene solution revealed the formation of the new product **7c**. It was found that the most appropriate reaction conditions to obtain samples of pure cycloadducts require heating of Feist's esters **1a**,**b** with *N*-phenylnitrones **6c–f** in benzene at 80 °C for 30–40 h; for the less reactive *N*-methylnitrones **6a**,**b** heating in toluene at 110 °C for 80 h is needed. Partial separation of the crude product mixtures on silica gel and subsequent crystallization from ethanol gave pure samples of new products **7** as single isomers in moderate yields of 20–60% (Scheme 3, Table 1). The separation is difficult when using more than 1 equiv. of nitrone due to its partial decomposition upon prolonged heating. The mixtures of the dimethyl ester of Feist's acid and *N*-phenylnitrones **6c–e** were also heated in C_6D_6 at 80 °C to study what other products were formed (Scheme 3). In ^{1}H NMR spectra we did not find additional signals arising from aliphatic protons or methoxycarbonyl group besides those of the unreacted Feist's esters and cycloadducts **7** (see Supporting Information).



Scheme 3. Cycloadditions between nitrones **6a**–**f** and Feist's esters **1a**,**b**.

Table 1. Results of reactions of nitrones **6** with Feist's esters **1**.

Nitrone **6**	R^1 [a]	R^2	R	Product/yield[b]
6a	Me	Ph	Me	**7a**/26%
6b	Me	4-Cl-C_6H_4	Me	**7b**/21%
6c	Ph	Ph	Me	**7c**/29%
6c	Ph	Ph	Et	**7d**/26%
6d	Ph	4-Cl-C_6H_4	Me	**7e**/48%
6e	Ph	4-MeO-C_6H_4	Me	**7f**/42%
6e	Ph	4-MeO-C_6H_4	Et	**7g**/59%
6f	Ph	2,4-Cl_2-C_6H_4	Et	**7h**/17%
6g	Ph	4-Br-C_6H_4	Me	**7i**/30%
6h	Ph	3-Br-C_6H_4	Et	**7j**/44%

[a] Reaction conditions: R^1 = Me, solvent toluene, 110 °C, 80 h; R^1 = Ph, solvent benzene, 80 °C, 30–40 h. [b] Isolated yields of pure samples after partial separation.

The structures of products **7** were established on the basis of their spectroscopic data (see Supporting Information). Thus, the ^1H NMR spectrum of **7c** shows two doublet signals of the cyclopropane ring at δ = 2.31 and 2.41 ppm with J = 5.8 Hz. This is consistent with the *trans*-disposition of the cyclopropane protons. The singlet signal of the methine proton C^3H appears at δ = 4.77 ppm, and the signals of the methylene group of the isoxazolidine ring C^5H_2 appear as two doublets at δ = 4.33 and 4.40 ppm with J = 8.7 Hz. The relative configuration of the products was established on the basis of ^1H-^1H NOESY NMR of the compound **7e**. In its spectrum cycloadduct **7e** exhibits interactions between the proton H^1 of the three-membered ring and both the methine proton of the isoxazolidine ring H^3 and the *ortho*-proton H^6 of the 4-chlorophenyl ring (Figure 2, structure **A**). In the alternative structure (Figure 1, structure **B**) the protons H^1 and H^6 are too far from each other for significant NOE interaction. The structure of the cycloadduct suggests the approach of a nitrone dipole from the least hindered side of the cyclopropane ring (Figure 2, **TS-A**). The unfavorable steric interactions between the methoxycarbonyl group of the cyclopropene ring and aryl substituent Ar of nitrones can occur in the alternative transition state (Figure 2, **TS-B**).

The obtained data demonstrates the significantly different behaviour of C=C-unsubstituted simple MCPs and esters of Feist's acid in the reaction with nitrones. Thus, in contrast to other C=C-unsubstituted MCPs, Feist's esters selectively yield only spiro[cyclopropane-1,4-isoxazolidines].

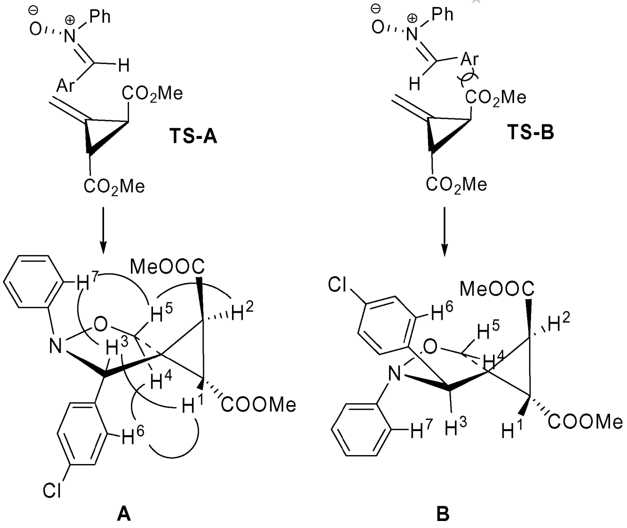


Figure 2. Structures of transition states **TS-A** and **TS-B** and the corresponding cycloadduct **A** (product **7e** with main NOE interactions in NOESY spectrum shown) and its possible isomer **B**.

The opposite regiochemical outcome (C-5 of the isoxazolidine forms the spiro atom) can be found in reactions of MCPs with electron-withdrawing groups directly at the C=C bond.[1e,17] Also, reactions with Feist's esters require elevated temperatures and prolonged reaction times, whereas C=C-unsubstituted MCPs are more reactive in cycloadditions with nitrones. Since the increase in steric bulkiness of MCPs should facilitates the formation of spiro[cyclopropane-1,5-isoxazolidine] isomers,[1e] we exclude steric factors as the possible explanation of the regiochemical outcome.

The combined data of the reactions of Feist's acid and its esters suggest that an inherent electronic effect in ring-acceptor-substituted MCPs is responsible for the obtained results. Molecular photoelectron spectroscopy in combination with theoretical calculations is known to be a useful method to study the electronic structure of molecules.[18a] The photoelectron spectra of a wide variety of π-systems and strained hydrocarbons have been investigated.[2b,18] However, the database of photoelectron spectra of MCPs is comparatively small and electron-acceptor substituted MCPs have apparently been overlooked.[18a] We have now analyzed the photoelectron spectrum of Feist's ester and investigated its electronic structure by quantum chemical methods.

The He^I photoelectron (PE) spectrum of the diethyl ester of Feist's acid **1b** is depicted in Figure 3. The relevant ionization potentials are summarized in Table 2 together with some results of quantum-chemical calculations for both unsubstituted MCP and the diethyl ester of Feist's acid. According to HF and B3LYP calculations both methoxycarbonyl groups in Feist's ester adopt a synperiplanar conformation so as to increase overlap of orbitals of an ester group and the three-membered ring. The known X-ray structure of Feist's acid supports the calculated geometry.[7b–7d]

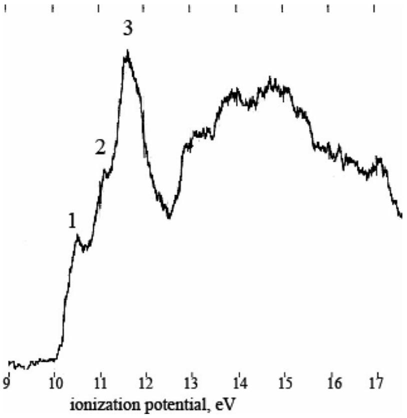


Figure 3. He^{I} photoelectron spectrum of **1b**.

Table 2. Ionization potentials IP/eV and orbital energies ε/eV of methylenecyclopropane MCP and diethyl ester of Feist's acid **1b**.

Compound	IP, assignment	$-\varepsilon^{HF[a]}$	$-\varepsilon^{B3LYP[b]}$	$IP_1^{B3LYP[c]}$
MCP	9.57, $\pi_{C=C}$[d]	9.78	6.86	9.63
1b	10.50, $\pi_{C=C}$, n_O	10.28	7.07	9.39
1b	11.12, ω_A–π_{CH2}, $n_{C=O}$	11.77	7.59	–
1b	11.53, $\pi_{C=O}$,n_{OMe}	12.01	7.72	–

[a] HF/6-31G*. [b] B3LYP/6-31G*. [c] Calculation of the first IP: energy difference of molecule and cation radical with identical geometry at B3LYP/6-31+G*. [d] Ionization potential taken from ref.[19]

The photoelectron spectrum of Feist's ester **1b** exhibits two weak and one strong broad bands (see Figure 3, bands 1, 2 and 3). Assignment of the first ionization potential can be achieved by means of Koopmans' theorem, $IP_i = -\varepsilon_i$, which relates vertical ionization energies to SCF MO energies.[20] According to HF/6-31G* calculations the HOMOs of both MCP and Feist's ester are $\pi_{C=C}$ orbitals located mainly on the carbon atoms of the exocyclic double bond with contribution from the lone-pair orbitals of oxygen atoms n_O in the case of Feist's derivative. The graphic representation of the HOMO of Feist's ester is given in Figure 4. Calculations at B3LYP level predict significant interactions of the $\pi_{C=C}$ orbital with lone pairs of oxygen atoms of the C=O bond $n_{C=O}$. This results in splitting into two new orbitals (Figure 4, HOMO and the third occupied MO). Ionization potentials and corresponding energies of HF orbitals show good agreement for both molecules (Table 2). Much better agreement between experimental and theoretical values can be expected for the first IP when the energies of the molecule and the cation-radical are calculated by the B3LYP method.[18a] Indeed, the first ionization potential derived from such calculations is in very good agreement with the experimental data for MCP, whereas B3LYP calculation fails to predict IP_1 of Feist's ester.[21] The assignment for higher ionization potentials is more difficult due to overlapping of several bands. HF and B3LYP calculations place orbital sequences in different order. The second occupied HF orbital of Feist's ester can be described as out-of-phase combination of antisymmetric Walsh orbital ω_A and the π_{CH2} orbital of the methylene group with contribution from lone pair orbitals of oxygen atoms n_O. However, the next four B3LYP orbitals have contributions mainly from lone pairs of oxygen atoms n_O and $\pi_{C=O}$ bonds of the carboxyl groups. Since B3LYP calculations fail to reproduce experimental IP_1, we tend to assign the second ionization potential to the removal of electron from the ω_A-π_{CH2} orbital. The strong band with ionization energy 11.52 eV (Figure 3, band 3) most likely arises from several ionization events. According to both HF and B3LYP calculations, the third band may belong to ejections of electrons from different orbitals with contributions of lone pairs of oxygen atoms of OEt fragment n_{OEt} and $\pi_{C=O}$ bonds.

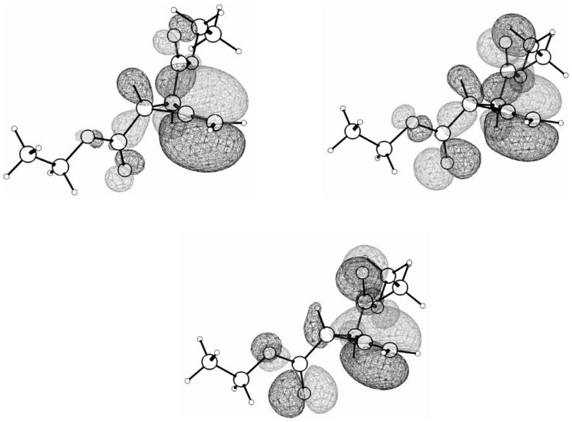
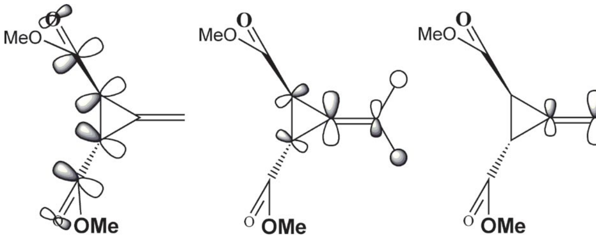


Figure 4. Graphical representation of the HOMO of Feist's ester **1b** (top, left: HF/6-31G*; top, right: B3LYP/6-31G*) and the 3rd occupied MO (bottom: B3LYP/6-31G*).

The obtained PE data demonstrate the significant lowering of the HOMO energy of Feist's ester **1b** by 0.93 eV. This suggests important changes in electronic structure by withdrawing electron density from exocyclic C=C bond to an electron-acceptor groups via the three-membered ring. Two electronic interactions were proposed by Houk to account for the angle distortion of the exocyclic methylene group in the acceptor-substituted at the three-membered ring MCPs: the first interaction proposed between the π* orbital of the substituent and a Walsh orbital of the cyclopropane ring.[6b] The second interaction proposed is between the π* orbital of the substituent and the π orbital of MCP. We also wish to emphasize the importance of interactions of different fragments with Walsh orbitals.[18a] According to the calculation results, the following interactions can contribute to the overall effect of the acceptor-substitution at the three-membered ring. The interaction between two π* orbital of the C=O bond and Walsh orbital ω_S involves transfer of electron density from the cyclopropane ring to the unoccupied orbital of the substituent (Figure 5, bonding $\omega_S+\pi^*_{C=O}$ combination shown). On the other hand, the interaction between the in-plane π_{CH2} orbital of the methylene group and ω_A Walsh orbital causes transfer of electron density from the methylene group to the cyclopropane ring (Figure 5, antibonding $\omega_A-\pi_{CH2}$ and bonding $\omega_A+\pi_{CH2}$

combinations shown). Thus, the overall effect is the decrease of electron density on the exocyclic methylene bond and its increased polarization.



$\omega_S+\pi^*_{C=O}$ $\omega_A-\pi_{CH2}$ $\omega_A+\pi_{CH2}$

Figure 5. Quantitative diagram of the interactions of Walsh orbitals in Feist's ester **1a**.

In a preliminary attempt to study the interaction of MCPs with nitrones, we have calculated the transition state structures of both regio-approaches of *C*,*N*-diphenylnitrone **6c** to parent MCP and Feist's ester **1a** at B3LYP/6-31G* level (see Supporting Information). The energy difference between the two regioisomeric transition states is 2.67 kcal/mol for MCP cycloaddition and 1.57 kcal/mol for Feist's ester. In both cases 5-isomeric transition states have lower free energy. The calculated activation free energies for cycloadditions of MCP and Feist's ester (5-regioisomeric transition states) are 44.30 and 45.68 kcal/mol, respectively (see Supporting Information). Thus, the obtained calculation data for MCP cycloaddition show good qualitative agreement with experimental results: the energy difference between the two regioisomeric transition states is small and favours the 5-isomer. However, B3LYP calculations do not account for decreased reactivity and inverse regioselectivity in the case of Feist's ester.[21]

Conclusions

In summary, the obtained data demonstrate the significant difference between ring-acceptor-substituted Feist's esters and simple MCPs. Previously obtained data reveal the lack of reactivity of Feist's acid and its derivatives with carbonyl ylides, peroxides and singlet oxygen, whereas simple MCPs give a number of different products. In this communication we have shown that nitrone cycloadditions to the C=C bond of Feist's ester stereoselectively leads to spiro[cyclopropane-1,4-isoxazolidines]. The reaction proceeds with the inverse regioselectivity and decreased reactivity. The measured photoelectron spectrum indicate considerable lowering of $\pi_{C=C}$ HOMO energy. This is the first example of a PE spectrum of a ring-acceptor-substituted MCP so far. Surprisingly, B3LYP calculations do not support the experimental findings. The qualitative diagram of the interactions of Walsh orbitals seems to account for the electronic effect in ring-acceptor-substituted methylenecyclopropanes. Further theoretical calculations of acceptor-substituted MCPs and their reactivity in different cycloaddition reactions are currently under investigation.

Experimental Section

General: Melting points were uncorrected. ^{1}H- and ^{13}C-NMR spectra were referenced to TMS in $CDCl_3$ solutions (300 and 75 MHz, respectively), and multiplicities of ^{13}C signals were determined by DEPT measurements. The photoelectron spectrum of compound **1b** was calibrated with Ar and Xe. A resolution of 20 meV was obtained for the $^2P_{3/2}$ line of Ar. IR spectra were measured as 2% solutions in $CHCl_3$ or CCl_4. Starting materials were prepared according to literature data: Feist's acid,[12] diethyl ester of Feist's acid,[12] dimethyl ester of Feist's acid was prepared by reaction of Feist's acid with Me_2SO_4 in Et_2O at room temperature, *C*-aryl-*N*-phenylnitrones **6c**–**f**,[22] *C*-aryl-*N*-methylnitrones **6a**,**b**.[23]

General Procedure for the Cycloaddition Reactions of Nitrones 6 with Feist's Esters 1a,b: The mixture of the corresponding nitrone **6a**–**f** (2 mmol) and Feist's ester **1a**,**b** (2 mmol) was heated at reflux for 30–40 h in dry benzene (nitrones **6c**–**f**) or for 80 h in dry toluene (nitrones **6a**,**b**). The solvent was removed under reduced pressure, and the products were isolated by chromatography of residue on silica gel eluting with a petroleum ether/ethyl acetate, 7:1 mixture. Pure samples were obtained by crystallization from ethanol. See Supporting Information for full details.

Computational Methods: All calculations were performed by using the *Gaussian98* program package.[24] Basis sets were used as implemented in *Gaussian98*. All transition states were characterized by their vibrational frequencies and all the reported thermodynamic data are given at 298.15 K from unscaled vibrational frequencies in the harmonic approximation.

Supporting Information (see also the footnote on the first page of this article): Full characterization data for compounds **7a**–**j**, copies of ^{1}H NMR spectra of reaction mixtures of nitrones **6c**,**g** and ester **1a**. Copies of ^{1}H- and ^{13}C-NMR spectra of compounds **7a**–**g**, **7i**–**j**. Copy of ^{1}H-^{1}H NOESY NMR spectrum of compound **7e**. Atomic coordinates for the optimized structures of methylenecyclopropane, Feist's esters **1a**,**b**, *C*,*N*-diphenylnitrone **6c** (B3LYP/6-31G*). Atomic coordinates for the transition state structures of the reaction of methylenecyclopropane and dimethyl ester of Feist's acid with *C*,*N*-diphenylnitrone **6c** (B3LYP/6-31G*), calculated thermochemical data (Table S1). Plot of several occupied molecular orbitals of methylenecyclopropane and dimethyl ester of Feist's acid (HF/6-31G*, B3LYP/6-31G*). Supporting Information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

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