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FIRST EXAMPLE OF DIELS-ALDER REACTION OF 4-(1-ETHENYLSUBSTITUTED)-3-METHYLISOXAZOLES WITH ACETYLENEDICARBOXYLATES

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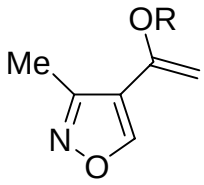
Abstract – The first example of a [4+2] cycloaddition reaction of 4-(1-ethenylsubstituted)isoxazoles with acetylenedicarboxylates is reported, while the corresponding 5-substituted isomers do not react with the same dienophile; density functional theory (DFT) calculation indicate the electronic origin of the different behaviour.

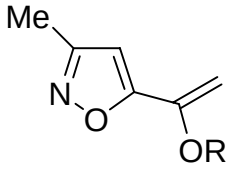
INTRODUCTION

Heteroaromatic silyl enol ethers derived from 2-acetyl-furan,[1] -thiophene,[1,2] and -pyrrole[3] were demonstrated to be useful dienes to undergo [4+2] cycloaddition reactions, but only one article appeared on the isomeric 3-substituted compounds.[4] In particular, there are no reports on this kind of reactivity of 4-(1-ethenylsubstituted)-isoxazoles and only two articles are reported for 5-vinylisoxazole.[5] Following our research in the chemistry of heterocycles, we investigated the possibility to use the isoxazole 4,5-double bond 4-vinyl group diene system as the enophile in a [4+2] cycloaddition reaction.[6]

We wish to report now the first example of such a reaction given by 4-[1-(methoxyethenyl]- (**1**) and 4-{1-[(trimethylsilyl)oxy]ethenyl}-3-methylisoxazole (**3**) with acetylenedicarboxylates showing that the corresponding 5-substituted isomers **2** and **4**, respectively, appear to be less reactive giving only traces of the cycloaddition products. At the same time no reactivity of both types of compounds was observed towards other dienophiles as maleic anhydride or *N*-phenylmaleimide.



1 R = Me
3 R = $SiMe_3$



2 R = Me
4 R = $SiMe_3$

RESULTS AND DISCUSSION

Diels-Alder reaction has proven to be one of the more reliable methods in preparative organic chemistry[7] and taking into consideration the easy isoxazole ring-opening[8] we wanted to check this type of reactivity on 3-methylisoxazoles **1-4** with the aim to report a new kind of reactivity of this heterocyclic system. We first investigated the reaction of compounds **1** and **2** with maleic anhydride but, whereas 3-methyl-5-vinylisoxazole reacts in very good yield (80%),[5a] both compounds do not gave rise to the desired cycloadducts. So, we focused our attention on acetylenedicarboxylate as dienophile, owing to the evident triple-bond's major electron density in comparison to that one of the double bond. Compound **1** reacts (Table 1, entry 1) with dimethyl acetylenedicarboxylate (DMAD) to give the expected cycloaddition reaction (Scheme 1).

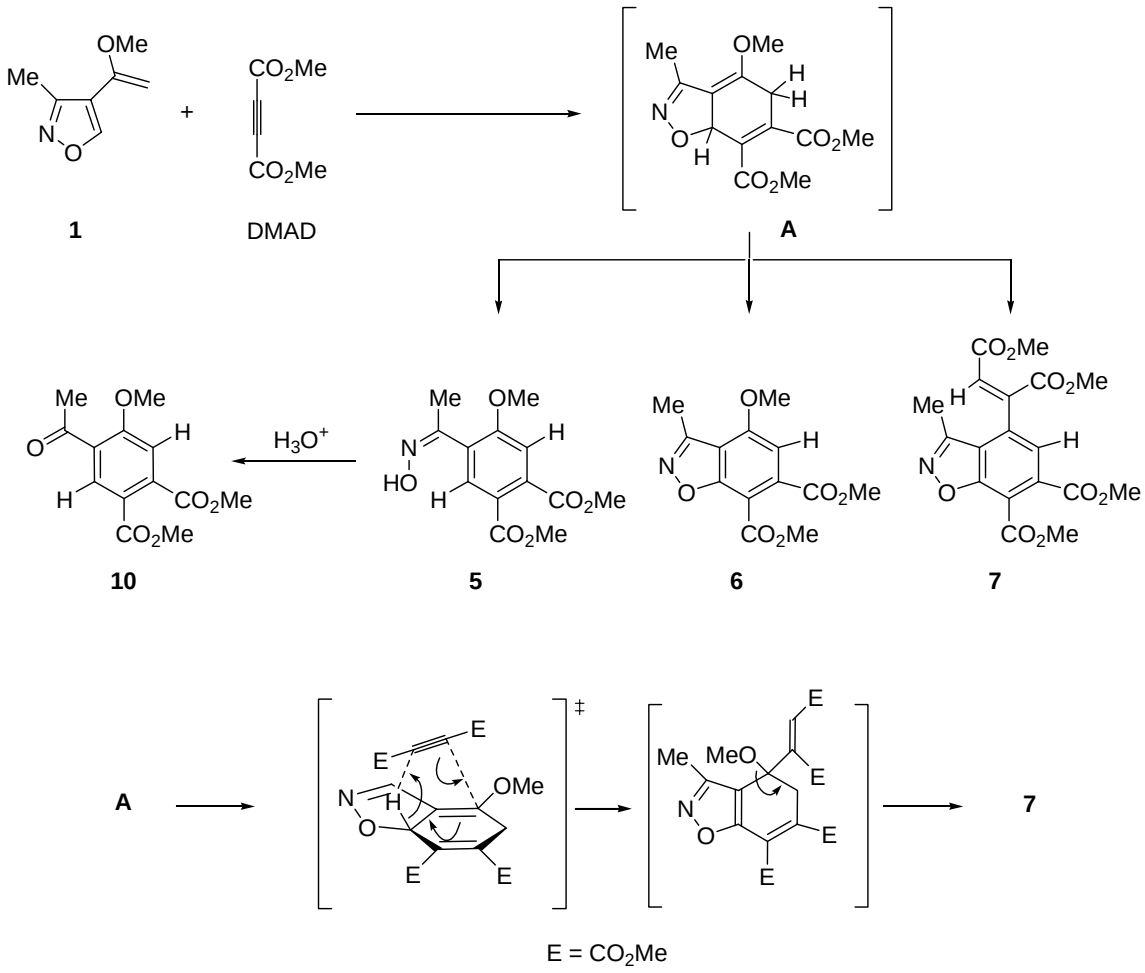
Table 1. Diels-Alder reaction of 1 with DMAD

Entry	T(°C)	Solvent	T(d)	%**5**[a]	%**6**[a]	%**7**[a]
1	80	-	0.2	20	15	15
2	rt	-	15	7	28	11
3	85	Benzene	1.3	12	8	12

[a] Yields of isolated products.

Compound **6** and the 1:2 adduct **7**, derived by the ene addition of a second molecule of DMAD to the adduct **A**1b (see Scheme 1), were obtained together with the oxime **5**, clearly originating from the isoxazole ring-opening (overall yield 50%); no reactivity of **6** with DMAD in the same experimental conditions was observed. The structures of all the isolated products were supported by analytical and spectroscopic data (MS, 1H- and 13C-NMR).

Trying to find the best conditions, we carried out the reaction at different temperatures and different reaction times without obtaining significant variations; in particular, at room temperature the starting product disappears after 15 days and from the mixture the same compounds **5-7** are obtained in 46% overall yield but with a different ratio (Table 1, entry 2). It is worthy to note that in the same conditions compound **2** did not react with DMAD and only in different experimental conditions (80 °C, benzene, 6 d) gave traces of the corresponding cycloadducts. In the last conditions, compound **1** showed a similar reactivity (Table 1, entry 3).



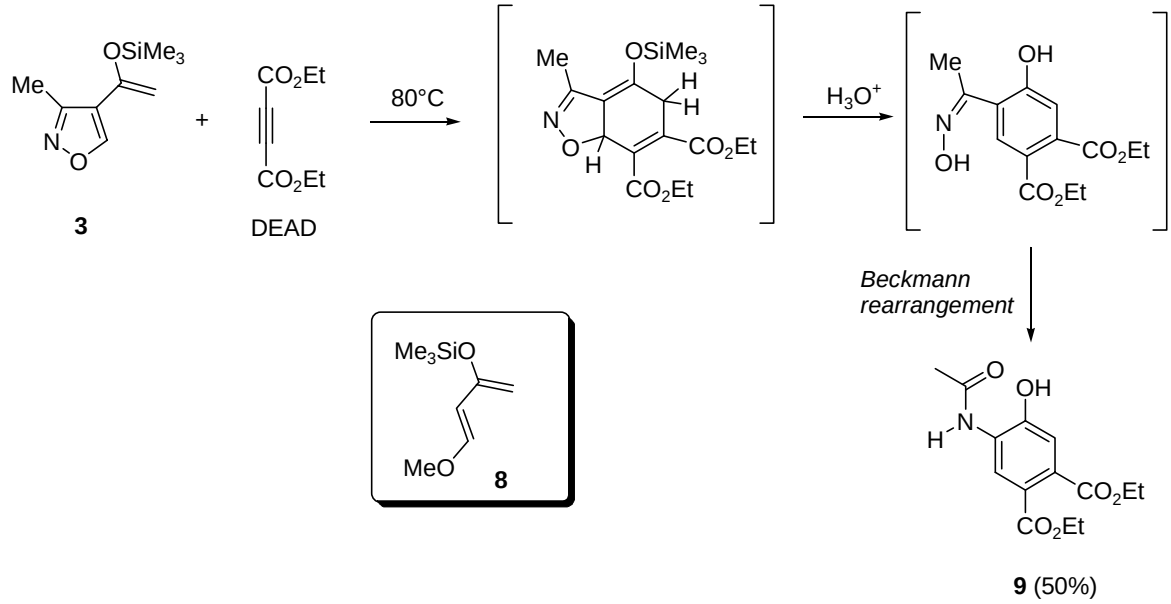
Scheme 1. Reactivity of compound 1 with DMAD

Scheme 1 shows the reaction pathway to compounds **5-7**. In particular, compound **6** arises by the exocyclic addition of the dienophile to the isoxazole 4,5-double bond 4-vinyl group diene system to give the adduct **A** which was then oxidized to the aromatic 1,2-benzisoxazole derivative **6**.

Following these results and taking in account the successful employment of 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (Danishefsky's diene) (**8**) in the synthesis of cyclohexenones[9] and in the total synthesis of natural products,[10] we tested the reactivity of silylenolethers **3** and **4** with DMAD and DEAD (diethyl acetylenedicarboxylate) under the same conditions employed for **8**.[9a,b]

Unfortunately, compounds **3** and **4** did not react with maleic anhydride in various conditions, the crude still containing the starting materials. When *N*-phenylmaleimide was used as the dienophile the same negative results were obtained also when operating under the conditions reported for 3-[1-(*tert*-butyldimethylsilyloxy)vin-1-yl]furan which affords good yields.[4] As for the reaction of compound **3** with DMAD and/or DEAD, several attempts were made varying the experimental conditions

according to the published methods for Diels-Alder reactions of trimethylsilyloxy derivatives.[9] Thus, only by carrying out the reaction without solvent at 80 °C for 2.5 h, the silyl enol ether **3** gave the acetylamino derivative **9** following the Beckmann rearrangement of the intermediate oxime (Scheme 2). Note that in acidic conditions oxime **5**, coming from reaction of **1** with DMAD, gave ketone **10** (Scheme 1), according to our recent results.[11]



Scheme 2. Reactivity of compound 3 with DEAD

In order to find a rationale for the absence of Diels-Alder reactivity for **2** and **4**, comparative DFT optimizations were carried out for the different isomers **1** and **2** in the gas phase (see Figure 1). The reliability of the calculations is confirmed by the consistency of the geometric parameters (especially those of the C=C-C=C butadiene moiety), with those of comparable structures (see for example ref. 12). As a most critical point, only the *trans*-butadiene conformation of **2** corresponds to a real minimum (**2**$_{\mathbf{min.}}$), which is about -4.6 Kcal mol^{-1} more stable than the isomer **1**. In contrast, the 180° rotated CHCOMe group, which would uniquely allow the [4+2] cycloaddition, is found to be a transition state (**2**$_{\mathbf{TS}}$, with one imaginary frequency). The energy barrier, likely due to the repulsion between the *in-plane* oxygen lone pairs, is +3.9 Kcal mol^{-1} and still allows rotation of the exocyclic group about the C-C bond (as confirmed by the NMR spectra). An incoming double or triple C-C bond must attack a structure like **2**$_{\mathbf{TS}}$ for the cycloaddition to occur and probably the lifetime of the latter is insufficiently long. From the orbital viewpoint, there is no apparent electronic obstacle for the concerted reaction, since the HOMO and LUMO of **2**$_{\mathbf{TS}}$ have qualitative features similar to those of **1** (see Figure 1). Thus, according to the Woodward and Hoffmann rules,[13] the HOMO is π bonding at the lateral C=C bonds but antibonding at the central one and electronic stabilization is attained upon is interaction with one vacant π^* level of the incoming C≡C unit. Conversely, the populated π level of the latter progressively destabilizes the LUMO, which features

in-phase p_π orbitals at the 1,4 carbon atoms. In conclusion, there is no symmetry forbidden HOMO-LUMO crossing along the reaction path, if the opportune conditions for the reaction are met by the reactant. This seems to be the case for **1** but not for **2**. Curiously, the 2-[1-(trimethylsilyloxy)ethenyl]furan undergoes cycloaddition reactions.[1] Comparative calculation show that the conformer with the shortest distance between the oxygen atoms is again a transition state but the barrier is about 1.5 Kcal mol^{-1} lower than that one for **2**. Although not very significant, the difference implies the TS structure to be slightly more accessible, hence the cycloaddition has more chances to occur.

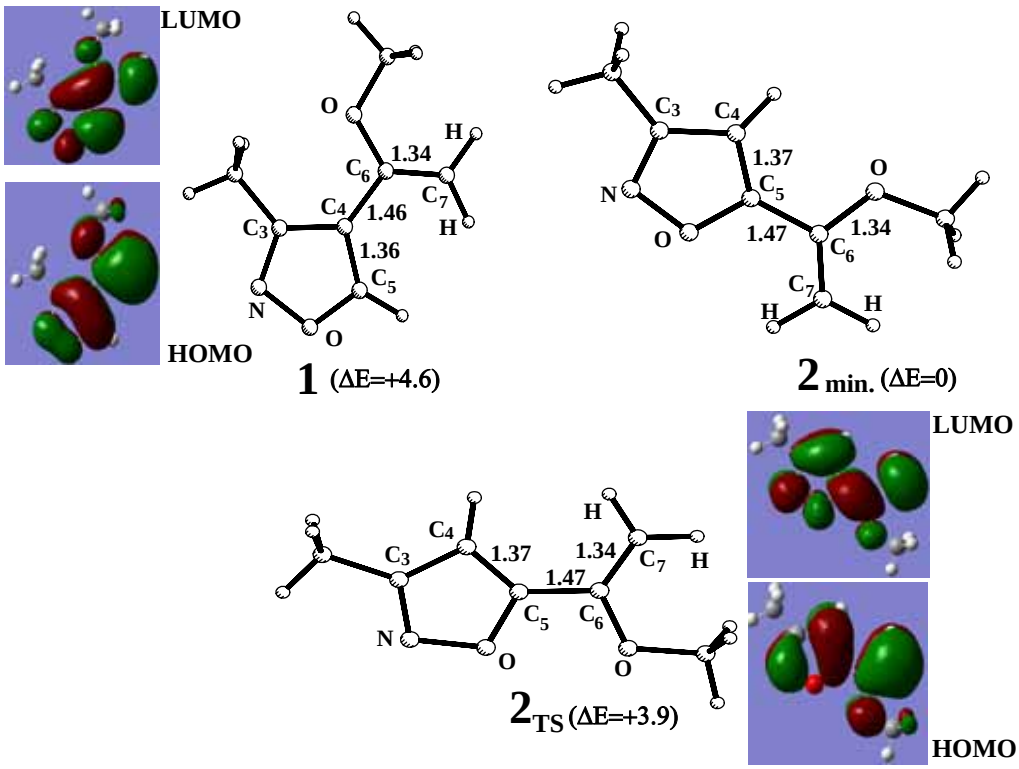


Figure 1. Optimized geometries of the isomers 1 and 2 and the transition state (2_{TS}) which features a 180° rotated methoxy-ethenyl group. The HOMO and the LUMO of 2_{TS} and 1 have comparable features

In summary, we conclude that 5-(1-alkoxy)vinyl derivatives of 3-methylisoxazole are less reactive than the corresponding 4-(1-alkoxy)vinyl- isomers and that the former are also less reactive of the corresponding 5-vinylderivative. This inferior reactivity can be rationalized on the basis of steric and electronic considerations that have a competitive effect: thus, the energy difference between the *s-cis* and the *s-trans* configurations is evidently smaller in the 5-vinylisoxazole with respect to the 1-alkoxyvinyl compound. Thus, we reported the first example of Diels-Alder reactions in which the diene part is represented by a 4-substituted isoxazole.

EXPERIMENTAL

Melting points were taken on a Büchi 510 apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer 881 spectrophotometer for dispersion in KBr. Elemental analyses were obtained by Elemental Analyzer Perkin-Elmer 240C Apparatus. Mass spectra were registered with a Carlo Erba QMD 1000 instrument at 70 eV. Compounds **1-4** were prepared as reported in the literature.[6] Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 230-400 mesh) were used for analytical TLC and for column chromatography, respectively. Solvent were removed under reduced pressure. All 1D and 2D NMR experiments were recorded at 25 °C on Varian Gemini-200 and Mercuryplus-400 with a 5 mm probe. Chemical shifts (δ in ppm) were given from solvent $CDCl_3$, 7.26 for ^1H and 77.00 for ^{13}C. All coupling constants are in Hz.

Cycloaddition reaction of 1 with dimethyl acetylenedicarboxylate (DMAD)

A mixture of **1** (0.834 g, 6.0 mmol) and DMAD (1.040 g, 7.3 mmol) was heated at 80 °C. The reaction was completed after 5 h. The reaction products were separated by chromatography (EtOAc/petroleum ether 40/70 = 1:1, as eluant). The first running band gave compound **7** (0.352 g, 0.9 mmol, 15%); the second one was compound **6** (0.251 g, 0.9 mmol, 15%); finally the third one gave compound **5** (0.337 g, 1.2 mmol, 20%). Spectroscopic data for dimethyl 4-(*N*-hydroxyethanimidoyl)-5-methoxybenzene-1,2-dicarboxylate (**5**): yellow wax; IR (KBr) 3650-2800, 1760, 1720, 1320 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.67 (s, 1H, H-3), 7.32 (s, exch., 1H, OH), 7.12 (s, 1H, H-6), 3.93 (s, 3H, CO_2Me), 3.91 (s, 3H, 5-OMe), 3.87 (s, 3H, CO_2Me), 2.14 (s, 3H, 1'-Me). ^{13}C NMR (50.30 MHz, $CDCl_3$) δ 168.5 (s, C=O), 166.5 (s, C=O), 158.05 (s, C-5), 153.1 (s, C=N), 135.77 (s, C-1/C-2), 130.3 (d, C-6), 126.2 (s, C-4), 122.3 (s, C-2/C-1), 110.8 (d, C-3), 56.1 (q, 5-OMe), 52.9 (q, CO_2Me), 52.5 (q, CO_2Me), 20.8 (q, 1'-Me); MS (EI) *m/z* (%): 281 (M^+, 27), 250 (100), 218 (56), 59 (22). Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.74; H, 5.24; N, 5.19. Spectroscopic data for dimethyl 4-methoxy-3-methyl-1,2-benzisoxazole-6,7-dicarboxylate (**6**): colorless solid; mp.143-144 °C (from EtOAc); IR (KBr) 1740, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H, H-5), 4.00 (s, 3H, 4-OMe), 3.97 (s, 3H, CO_2Me), 3.93 (s, 3H, CO_2Me), 2.63 (s, 3H, 3-Me); ^{13}C NMR (100.58 MHz, $CDCl_3$) δ 167.7 (s, 6-CO_2Me), 164.4 (s, 7-CO_2Me), 162.4 (s, C-7a), 157.3 (s, C-4), 154.7 (s, C-3), 136.85 (s, C-6), 114.55 (s, C-3a), 107.7 (s, C-7), 103.9 (d, C-5), 56.3 (q, 4-OMe), 53.1 (q, CO_2Me), 52.7 (q, CO_2Me), 11.7 (q, 3-Me); MS (EI) *m/z* (%): 279 (M^+, 52), 248 (100). Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.69; N, 5.02. Found: C, 56.06; H, 4.75; N, 4.81. Spectroscopic data for dimethyl 4-[(1*Z*)-3-methoxy-1-(methoxycarbonyl)-3-oxoprop-1-en-1-yl]-3-methyl-1,2-benzisoxazole-6,7-dicarboxylate (**7**): yellow wax; IR (KBr) 2984, 1725, 1370 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.76 (s, 1H, H-5), 6.19 (s, 1H, C=CH), 4.05 (s, 3H, CO_2Me), 3.96 (s, 3H, CO_2Me), 3.86 (s, 3H, CO_2Me), 3.84 (s, 3H, CO_2Me), 2.59 (s, 3H, 3-Me). ^{13}C NMR (50.30 MHz, $CDCl_3$) δ 165.7 (s, C=O), 165.6 (s, C=O), 164.4 (s, 2xC=O), 160.2 (s, C-7a), 154.6 (s, C-3), 140.9 (s, C-1'), 132.0 (s, C-4), 131.3 (s, C-6), 127.9 (d, C-2'),

124.3 (d, C-5), 123.1 (s, C-3a), 117.4 (s, C-7), 53.3 (q, CO_2Me), 53.2 (q, 2xCO_2Me), 52.6 (q, CO_2Me), 12.0 (q, 3-Me); MS (EI) *m/z* (%): 391 (M^+, 14), 360 (94), 300 (100), 59 (19). Anal. Calcd for $C_{18}H_{17}NO_9$: C, 55.25; H, 4.38; N, 3.58. Found: C, 55.09; H, 4.58; N, 3.34.

Cycloaddition reaction of 3 with diethyl acetylenedicarboxylate (DEAD)

A mixture of **3** (0.197 g, 1.0 mmol) and DEAD (0.340 g, 2.0 mmol) was heated at 80 °C for 2.5 h under air pressure, dissolved in Et_2O (4 mL) including *p*-toluenesulfonic acid monohydrate (0.190 g, 1.0 mmol) and stirred overnight at rt. The solution was poured into water (10 mL) and extracted with Et_2O (4x5 mL). The extracts were dried over sodium sulfate and evaporated. Pure compound **9** (diethyl 4-(acetylamino)-5-hydroxybenzene-1,2-dicarboxylate) (0.140 g, 0.5 mmol, 50%) was obtained by flash-chromatography (EtOAc/petroleum ether 40-70 = 1:4, as eluant); colorless wax; IR (KBr) 3600-3000, 2960, 1745, 1720, 1325 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 11.63 (s, exchangeable, 1H, OH), 7.96 (s, 1H, H-3), 7.52 (s, exchangeable, 1H, NH), 7.09 (s, 1H, H-6), 4.36 (q, 2H, *J* = 7.1 Hz, OCH_2Me), 4.32 (q, 2H, *J* = 7.1 Hz, OCH_2Me), 2. 37 (s, 3H, 2'-Me), 1.35 (t, 3H, *J* = 7.1 Hz, OCH_2Me), 1.34 (t, 3H, *J* = 7.1 Hz, OCH_2Me). ^{13}C NMR (50.30 MHz, $CDCl_3$) δ 168.0 (s, C=O), 166.2 (s, C=O), 160.6 (s, C-2'), 158.6 (C-5), 136.3 (s, C-4), 129.9 (d, C-6), 120.5 (s, C-1/C-2), 119.6 (s, C-2/C-1), 117.35 (d, C-3), 61.8 (t, OCH_2Me), 61.4 (t, OCH_2Me), 14.1 (q, OCH_2Me), 14.0 (q, OCH_2Me), 10.8 (q, 2'-Me); MS (EI) *m/z* (%): 295 (M^+, 36), 250 (54), 222 (69), 204 (100), 177 (32), 132 (40). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.83; H, 5.94; N, 4.91.

Computational Details

Structural optimisations were carried out at the hybrid density functional theory (DFT) using the Gaussian03 program.[14] The method used was the Becke's three-parameter hybrid exchange-correlation functional containing the nonlocal gradient correction of Lee, Yang and Parr (B3LYP).[15,16] The nature of the optimised structures were confirmed by calculations of the frequencies. The basis set used for the remaining atomic species was the 6-31G(d, p).[17]

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