Journal of Molecular Structure 1010 (2012) 158–168

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Diels–Alder reactions for the rational design of benzo[*b*]thiophenes: DFT-based guidelines for synthetic chemists

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ARTICLE INFO

Article history:
Received 9 August 2011
Received in revised form 25 November 2011
Accepted 25 November 2011
Available online 8 December 2011

Keywords:
Nitrothiophenes
Substituted 1,3-butadienes
Benzo[*b*]thiophenes synthesis
Polar Diels–Alder reactions
DFT-based descriptors
Reaction mechanism

ABSTRACT

In this work we studied the capability of several diene/dienophile pairs to undergo Diels–Alder (DA) reactions leading to benzo[*b*]thiophenes. A variety of synthetically and commercially available nitrothiophenes were chosen as dienophiles. Methyl 5-nitro-3-thiophenecarboxylate was selected as a potential strong electrophilic candidate based on some DFT-based properties and the substitution pattern of the expected product. The mechanistic details concerning the participation of this dienophile in polar DA reactions were investigated through a theoretical point of view. The results were compared with the experimental outcomes. This methodology should allow synthetic chemists to analyze DA reactions in detail in a stage prior to the synthetic job.

1. Introduction

Benzo[*b*]thiophenes constitute many natural products as well as pharmaceuticals, herbicides, dyes, and other products of technical importance [1]. For example, 4-(*N*-methylcarbamoyl) benzo[*b*]thiophene (mobam), which is bioisosteric with its naphthalene analog, is an effective insecticide [2]; [2-(4-hydroxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy] phenyl]-methanone hydrochloride (raloxifene hydrochloride) is an estrogen agonist/antagonist, commonly referred to as a selective estrogen receptor modulator [3]; benzo[*b*]-3-thienylacetic acid promotes the growth of plants and 3-(2-aminoethyl)benzo[*b*]thiophene is known to have a strong action on the central nervous system, with an activity higher than that of its indole analog [4]. Moreover, many dyestuffs and promising switches are derived from benzo[*b*]thiophene [4,5].

The construction of fused heterocycles can be accomplished in a simple way through the utilization of suitable heterocyclic ring systems in thermal DA reactions (Fig. 1) [6]. When the aromatic systems are intended to be used as dienophiles, they should be correctly functionalized in order to be activated towards this kind of DA reactions [7].

Due to the importance of benzo[*b*]thiophene derivatives and taking into consideration the utilization of 5-membered heterocycles to build fused heterocyclic systems, we decided to investigate some DA reactions involving a variety of electron-deficient thiophenes and some electron-rich dienes using Density Functional Theory (DFT) methods.

The main purpose of this work is to elucidate the feasibility of the proposed reactions, to establish reactivity trends, to suggest potentially reactive pairs and to validate the theoretical predictions by experimental work. Therefore, we intend to propose simple guidelines that can be useful for synthetic practitioners in order to select the most appropriate reactants.

2. Computational and experimental section

2.1. Computational details

The gas-phase equilibrium geometries of all species described here were obtained by full optimization at the B3LYP/6-31G(d) level [8] using GAUSSIAN03 program [9]. This level of theory was chosen because it was shown to be adequate to model DA reactions concerning medium-sized molecules [10] and also allows that the calculations performed here were done in a reasonable time.

All stationary points found were characterized as true minima by frequency calculations. Transition states were further characterized

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doi:10.1016/j.molstruc.2011.11.050

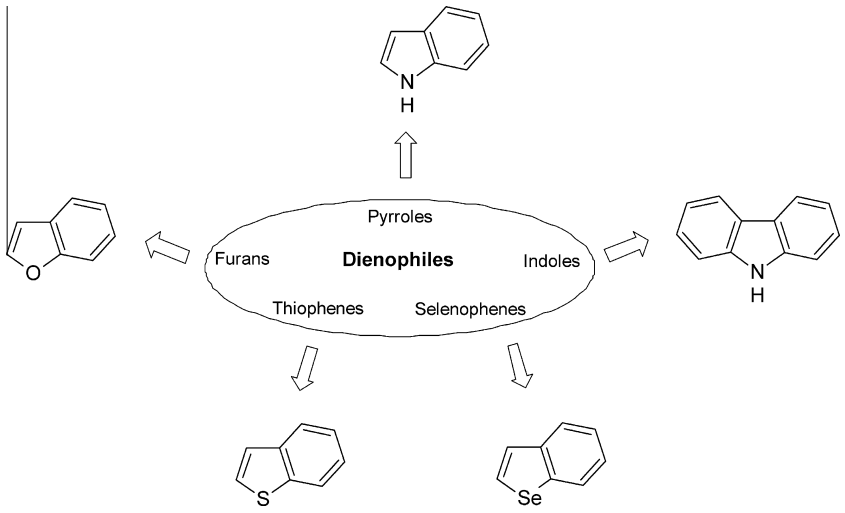


Fig. 1. Participation of selected heterocycles as dienophiles in thermal DA reactions.

by intrinsic reaction coordinate (IRC) calculations [11] (15 points along both directions of the normal mode corresponding to the imaginary frequency). All B3LYP/6-31G(d) calculated energies were corrected for zero-point vibrational effects (ZPE) and the free energy changes were derived from the sums of the electronic and thermal Gibbs free energies. Zero-point energies and thermal corrections are unscaled.

Solvent effects on the reaction mechanism were considered by single-point (SP) calculations on the gas-phase optimized structures using a self-consistent continuum method [12] in its conductor-like approximation (CPCM) [13]. Only the electrostatic component of the solvation energy was taken into account. The solvent used was benzene because it is the common solvent in which most of this kind of DA reactions is carried out.

Calculated gas-phase free energies (i.e. ΔG°) use a standard-state gas-phase pressure of 1 atm and solution-phase free energies (i.e. ΔG^{*}) use a standard-state solution-phase concentration of 1 mol/L. Therefore, for the standard state conversion from gas-phase to solution a value of 1.9 kcal mol^{-1} (2.8 kcal mol^{-1}) was subtracted from the SP/CPCM ΔG^{*}_{act} and ΔG^{*}_{reac} at 298 K (433 K) [14].

Different DFT-based indexes [15] were calculated in order to model the chemical reactivity in these polar DA reactions [15b]. For instance, the chemical hardness (η) was approximated in terms of the energies of the HOMO and LUMO frontier molecular orbitals (FMO) according to Eq. (1) and the electronic chemical potential (μ) was calculated using Eq. (2) [16]:

$$\eta = (\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}) \tag{1}$$

$$\mu = (\varepsilon_{\mathrm{LUMO}} + \varepsilon_{\mathrm{HOMO}})/2 \tag{2}$$

The global electrophilicity index (ω), which is a useful descriptor of reactivity that allows a quantitative classification of the global electrophilic character of a molecule within a unique relative scale, was calculated using Eq. (3) [17]:

$$\omega = \mu^2/2\eta \tag{3}$$

In order to characterize the electron-rich species, the global nucleophilicity index (N) was calculated using Eq. (4) [18]:

$$N = (\varepsilon_{\mathrm{HOMO,Nu}} - \varepsilon_{\mathrm{HOMO,TCE}}) \tag{4}$$

where $\varepsilon_{\mathrm{HOMO,TCE}}$ is the HOMO energy of tetracyanoethylene (TCE) (taken as a reference molecule).

Another parameter that was used as a reactivity descriptor is the polarizability, which measures the relative tendency of the electronic cloud of a chemical species to be distorted from its normal shape by a weak external electric field [19]. The mean value was calculated using the following equation:

$$\alpha = (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})/3 \tag{5}$$

where α_{xx}, α_{yy} and α_{zz} are the diagonal components of the polarizability tensor.

Local reactivity descriptors, which reflect the sites in a molecule where the reactivity pattern stated by the global quantities should take place, were also computed. For example, regional Fukui functions [20] were obtained from SP calculations on the optimized structures of the reactants, using different levels of theory and basis sets. The condensed Fukui function (Eq. (6)) [21,22] for electrophilic (nucleophilic) attack involves the HOMO (LUMO) FMO coefficients (c) and the atomic overlap matrix elements (S). This scheme has been corroborated for several reactions that are well documented [23]:

$$f_k^{\alpha} = \sum_{\mu \in k} |c_{\mu\alpha}|^2 + \sum_{\nu \neq \mu} c_{\mu\alpha} c_{\nu\alpha} S_{\mu\nu} \tag{6}$$

A program that reads the FMO coefficients and the overlap matrix from the Gaussian output files and performs the required calculation was used [24].

Subsequently, other local reactivity parameters were introduced (e.g. electrophilicity [25] and nucleophilicity [26]). Therefore, in order to analyze at which atomic site of the dienophile molecule the maximum electrophilicity power will be developed, Eq. (7) was used [25]:

$$\omega_k = \omega f_k^{+} \tag{7}$$

On the other hand, with the purpose of identifying the most nucleophilic site of the diene molecules, the nucleophilicity index was calculated using Eq. (8). In this way, the activation caused by different substituents on 1,3-butadiene derivatives was assessed:

$$N_k = N f_k^{-} \tag{8}$$

where N is the global nucleophilicity index [18] and N_k is its local counterpart [26].

B3LYP calculations indicate that the *s-trans* conformations of the dienes are more stable than the *s-cis* counterparts (Table 1). The *s-cis* structures, which show slight deviation from planarity due to steric effects, are needed to carry out the DA reactions.

Table 1
Relative energies (B3LYP/6-31G(d) + ZPE) (in kcal mol^{-1}) and dihedral angles $C_{1'}$-$C_{2'}$-$C_{3'}$-$C_{4'}$ (in degree).

Diene	Gas-phase		Benzene	
	ΔE	Dihedral angle	ΔE	Dihedral angle
1	3.4	31.1	3.7	30.4
2	5.1	29.7	5.3	29.2
3	3.0	33.2	2.6	33.1
4.1	2.7	28.6	3.2	27.9
4.2	3.7	34.1	3.8	34.6
5	3.1	26.0	3.3	23.7
Butadiene	3.5	30.3	3.5	29.2

Therefore, these conformations were used for the computational studies.

2.2. General experimental details

NMR spectra were recorded at 298 K in $CDCl_3$, using TMS as the internal standard. GC–MS analyses were performed in an instrument equipped with a 100% polydimethylsiloxane column. IR spectra were recorded from KBr pellets (as in the case of solids) and from thin films over KBr disks (as in the case of liquids). Silica gel (70–230 mesh) and alumina (150 mesh) were used for chromatography. The reaction solvent (benzene) was first dried over calcium chloride and then, over sodium wires. Finally, it was refluxed over metallic sodium for some days immediately before use. Diazomethane (in ether) was prepared *in situ* starting from *N*-nitroso-*N*-methylurea [27], this precursor was synthesized from urea and methylamine following the literature methods [28].

2.3. Synthetic procedure

Compound **10** was prepared by a sequence of reactions starting from the commercially available 3-thiophenecarboxylic acid [29]. First of all, a derivatization reaction employing diazomethane was done in order to obtain the methyl ester. Since ester substituents deactivate the aromatic rings towards electrophilic substitution reactions, fumic nitric acid in acetic anhydride was employed to nitrate the heterocyclic compound.

2.4. Methyl 5-nitro-3-thiophenecarboxylate (*10*)

An ethereal solution of diazomethane (prepared by literature methods) [27] was slowly added to a cold mixture of 3-thiophenecarboxylic acid (5.0 g, 39 mmol) in ether (10 mL) (caution: diazomethane is explosive and highly toxic. Avoid using sharp materials). When the evolution of the nitrogen liberated in the reaction finished and the excess of diazomethane was noted (yellow color), no more diazomethane was added. The reaction mixture was stirred for 2 h in an ice-water bath and for 2 h at room temperature to insure complete reaction. The solution was filtered and the ether and excess of diazomethane were evaporated under reduced pressure. The viscous residue was dissolved in dichloromethane and dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated to give an oil. The complete disappearance of the substrate was checked by silica gel TLC. In the TLC plate the product was visualized by UV light and also by *p*-dimethylaminobenzaldehyde solution [30] (color of the spot: reddish); R_f (hexane/ethyl acetate 2:1) = 0.72. Identification data: IR (KBr) ν (cm^{-1}): 1718, 1352; ^{1}H NMR (300 MHz, Cl_3CD) δ (ppm): 8.10 (dd, 1H, J = 3.0, 1.2 Hz), 7.52 (dd, 1H, J = 5.1, 1.2 Hz), 7.30 (dd, 1H, J = 5.1, 3.1 Hz); 3.87 (s, 3H). ^{13}C NMR (200 MHz, Cl_3CD) δ (ppm): 163.2, 132.6, 130.8, 128.8, 127.8, 52.8.

A mixture of acetic anhydride (15.7 mL, 166 mmol) and fuming nitric acid (1.8 mL, 44 mmol) was cooled to −14 °C and a cold solution of methyl 3-thiophenecarboxylate (4.8 g, 34 mmol) in acetic anhydride (15.7 mL, 166 mmol) was slowly added to the reaction mixture keeping the temperature at −12 °C. The reaction mixture was stirred for 4 h and was allowed to stand overnight at room temperature. The mixture was poured into ice-water (final volume: 150 mL), neutralized with a saturated solution of sodium bicarbonate (150 mL) and extracted with diethyl ether (10 × 30 mL). The combined ethereal phases were washed with cold water (15 mL) and dried over sodium sulfate. The reaction was checked by silica gel TLC (hexane/ethyl acetate 2:1). The nitrated product was visualized by UV light and also by *p*-dimethylaminobenzaldehyde solution. After some hours subsequent to the heating of the plate, the compound was visualized as a yellow spot; R_f (hexane/ethyl acetate 2:1) = 0.57. Column chromatography over silica gel (hexane/ethyl acetate 10:1) of the evaporation residue gave **10** as a pale yellow solid (yield: 2.2 g, 35%). Identification data: IR (KBr) ν (cm^{-1}): 1343, 1534, 1717; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.28 (1H, d, J = 1.8 Hz), 8.24 (1H, d, J = 1.8 Hz), 3.91 (3H, s); ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm): 51.6, 131.3, 134.8, 142.7, 153.2, 160.0; MS (EI) *m*/*z* 187 (M^+), 156 (100), 141, 110, 82.

Dienes **1** and **3** are commercially available [31], whereas diene **4** was prepared following the procedure proposed by Oppolzer et al. [32] without isolation of the imine intermediate, and with subsequent purification by column chromatography over silica gel using hexane/ethyl acetate [33,34].

The DA reactions were performed under conditions similar to those reported for nitronaphthalenes [33,35]. The reaction temperature was 160 °C using benzene as solvent. The molar diene/dienophile ratio was 2:1 for **1**; 2.5:1 for **4** and 6:1 for **3**.

General procedure for the thermal DA reactions: All reactions were carried out in oven-dried glassware. An ampoule containing a solution of 1.0 mmol of the dienophile and the required amount of the diene in 0.5 mL of dry benzene was cooled in liquid nitrogen, sealed and heated in an oil bath. After completion of the reaction, it was cooled once more in liquid nitrogen and opened. The solvent was evaporated *in vacuo* to give the crude product, which was subjected to TLC and GC–MS spectrometry. For the case in which the reaction yield was moderate (i.e. DA reaction between **10** and **1**), column chromatography and NMR analysis were also performed.

*Methyl benzo[b]thiophene-3-carboxylate (**27**).* Detected by GC–MS of the reaction crude. MS (EI) *m*/*z*: 192 (M^+), 177, 161, 133, 45, 89.

Methyl 7-(N-propylacetamido)-4,7-dihydrobenzo[b]thiophene -3-carboxylate (***25***). Detected by GC–MS of the reaction crude. MS (EI) *m*/*z*: 293 (M^+), 278, 262, 250, 218, 193.

*Methyl 5-hydroxybenzo[b]thiophene-3-carboxylate (**28**).* Detected by GC–MS of the reaction crude. MS (EI) *m*/*z*: 208 (M^+), 193, 179, 178, 177, 149. Column chromatography over alumina (hexane/ethyl acetate mixtures) of the crude product gave **28** (42%). IR (KBr) ν (cm^{-1}): 3369 (br), 1712, 1358; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.96 (3H, s), 5.91 (1H, br s), 7.03 (1H, dd, J = 8.4, 2.4 Hz), 7.72 (1H, d, J = 8.4 Hz), 8.13 (1H, d, J = 2.4 Hz), 8.39 (1H, s); ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm): 51.9, 109.6, 115.3, 123.4, 126.1, 132.2, 138.1, 138.2, 154.5, 163.6.

3. Results and discussion

3.1. Selection of the dienes and dienophiles

Thiophene derivatives were chosen in view of examining its reactivity towards electron-rich 1,3-butadienes. Therefore, in order to test the efficacy of this kind of compounds to undergo DA

reactions, the following dienes (Fig. 2), commonly used in polar DA reactions, were selected.

They have been demonstrated to undergo DA reactions with a wide range of dienophiles with complete regiocontrol [36]. Another feature that makes them especially useful in organic synthesis is the possibility to obtain aromatic products under certain experimental conditions, by losing the substituents that are initially placed in strategic positions of the 1,3-butadiene system and in the dienophile as well (Scheme 1) [33,37].

1-*N*-acylamino-1,3-butadienes are very convenient synthetic equivalents for the parent 1-amino-1,3-butadienes. These electron-rich dieneamides undergo DA reactions with high regio- and stereoselectivity [38].

The electrophilic activation of the thiophene ring towards DA reactions can be achieved by the incorporation of electron-withdrawing substituents. Since nitro is one of the most powerful electron-withdrawing groups, it is an opportune substituent to induce polar DA reaction towards electrophilic activation of the π system to which it is directly attached. Therefore, substitutions with a nitro group exclusively and in combination with other electron-withdrawing substituents were considered.

The substitution patterns concerning the dienophile were chosen based on published synthetic procedures and commercial availability (Refs. [41–54] in Table 2). Nitroethylene, a well known powerful dienophile is included in Table 2 as a reference dienophile [39,40]. Thiophene is also considered in order to do comparisons.

As expected, the substitution of one hydrogen atom in the thiophene ring (**20**) by one nitro group increases the electrophilicity character. A larger effect is found in the 2-nitro-substituted heterocycle (**13**) compared with the 3-nitro-substituted derivative (**18**). The disubstitutions considered in Table 2 are also suitable in order to enhance the reactivity of the dienophiles.

The thiophene rings substituted with two different electron-withdrawing groups (i.e. methyl carboxylate/cyano/bromine and nitro at C_2) show the highest values in electrophilicity power (ω = 2.83–3.65 eV). Consequently, these strong electrophiles are tentatively considered as possible dienophiles.

It is important to notice that subsequent HNO_2 elimination from the cycloadducts is necessary to promote aromatization. This step requires an H atom as neighbor to the NO_2 (i.e. adjacent to the nitro-substituted carbon of the thiophene ring). Therefore, substitution by two groups in adjacent positions (e.g. C_2 and C_3 or C_4 and C_5) will prevent subsequent aromatization of the cycloadducts.

For that reason (lacking a H atom neighboring the NO_2 group) and/or low electrophilicity, compounds **8** and **11**–**19** are discarded.

On the other hand, thiophenes **6**, **7**, **9** and **10** are potential candidates to act as electrophiles in polar DA reactions. Due to dissimilar positional relation of the substituents in these compounds, two classes of benzo[*b*]thiophenes will be obtained after nitrous acid elimination and aromatization from the cycloadducts (i.e. 2-substituted and 3-substituted benzo[*b*]thiophenes). The substitution pattern that could allow the construction of simple 3-substituted benzo[*b*]thiophenes, which have important applications [4,55,56] is the one displayed in compound **10** (Fig. 3). In contrast, the other 3 dienophiles could allow obtaining the basic benzo[*b*]thiophene skeleton that is part of more complex structures in which the 2 position is substituted by different groups (Fig. 4) [57–59].

Considering Figs. 3 and 4, we decided to analyze compound **10** that allows obtaining the heterocyclic structure of simple benzo[*b*]thiophenes through DA reactions and then, just by means of functional group transformations on the methyl ester fragment, important compounds could be obtained in a simple way. On the other hand, the compounds depicted in Fig. 4 are more complex in structure. Hence, not only functional group transformations will be required in the synthetic strategies.

So, compound **10** was chosen to be investigated in polar DA reactions with a variety of dienes. This substitution pattern is suitable in order to guarantee a good electrophilic behavior of the dienophile and to allow the aromatization process to take place. Moreover, this dienophile can be easily synthesized starting with the carboxylic ester or with the carboxylic acid (both commercially available).

Considering the substitution pattern of the reacting pairs (i.e. dienes with electron-releasing groups and dienophile with electron-withdrawing groups), it can be clearly seen that these DA reactions have a polar nature [15b], in which the thiophene derivative acts as a strong electrophile, and the dienes as strong nucleophiles. In fact, the dienophile, with an electrophilicity power of 2.84 eV, can be classified as a strong electrophile within the scale of electrophilicity proposed by Domingo et al. [40], and the dienes (N = 3.67–4.31 eV, Table 3, Fig. 5) can be classified as strong nucleophiles [18].

On the other hand, the electronic chemical potential of the diene series (Table 3) is higher than that of the dienophile (−5.23 eV), thereby suggesting that the net charge transfer will take place from the diene towards the thiophene derivative. This also indicates that the dienes will more likely behave as electron donor species (i.e. as nucleophile).

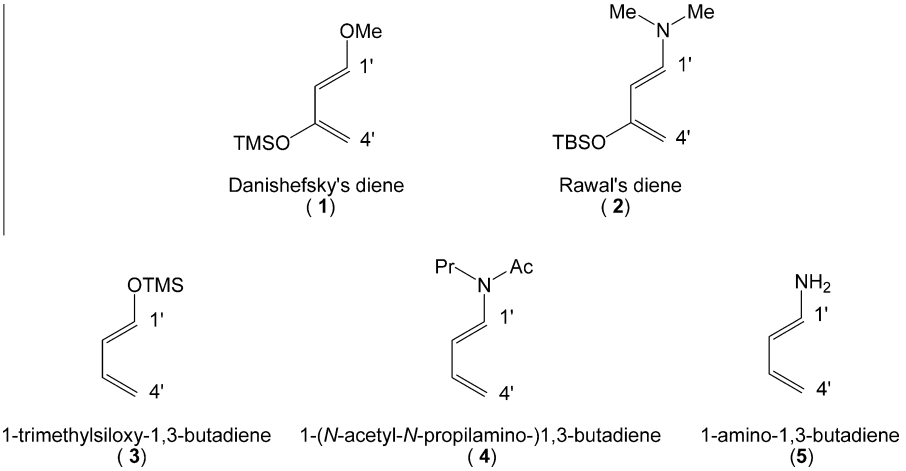
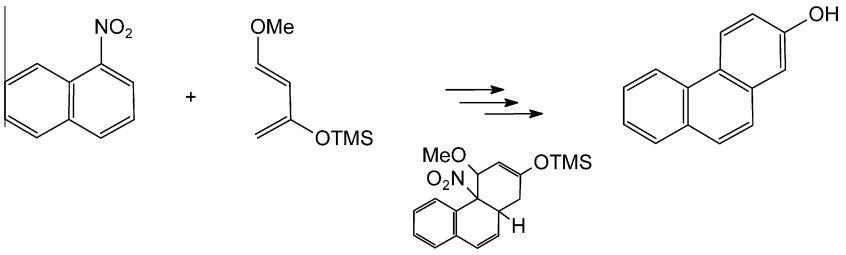


Fig. 2. Selected 1,3-butadienes.



Scheme 1. Aromatization of the cycloadduct in the thermal DA reaction between 1-nitronaphthalene and 1-methoxy-3-trimethylsiloxy-1,3-butadiene [33].

Table 2
B3LYP/6-31G(d) calculated global reactivity indexes, electronic chemical potential μ, chemical hardness η, and electrophilicity ω, for the considered dienophiles.

Molecule	Global properties (eV)		
	μ	η	ω
Methyl 2-cyano-5-nitrothiophene [41] (**6**)	−5.66	4.39	3.65
Methyl 5-nitrothiophene-2-carboxylate [42] (**7**)	−5.34	4.50	3.16
Methyl 2-nitrothiophene-3-carboxylate [43] (**8**)	−5.19	4.61	2.92
2-Bromo-5-nitrothiophene [44] (**9**)	−5.02	4.32	2.91
Methyl 5-nitrothiophene-3-carboxylate [45] (**10**)	−5.23	4.81	2.84
2-Nitro-3-bromothiophene [46] (**11**)	−5.06	4.51	2.83
Methyl 3-nitrothiophene-2-carboxylate [47] (**12**)	−5.04	4.70	2.70
2-Nitrothiophene [48,49] (13)	−4.90	4.62	2.66
Methyl 4-nitrothiophene-2-carboxylate [50] (**14**)	−5.09	4.98	2.60
Nitroethylene [40] (reference dienophile) (**15**)	−5.33	5.44	2.61
2-Nitro-3-methylthiophene [51] (**16**)	−4.86	4.70	2.51
Methyl 4-nitro-5-methylthiophene-2-carboxylate [52] (**17**)	−4.84	4.83	2.42
3-Nitrothiophene [48,53] (**18**)	−4.88	4.95	2.40
2-Methyl-3-nitrothiophene [54] (**19**)	−4.62	4.78	2.23
Thiophene (**20**)	−4.08	4.35	2.07

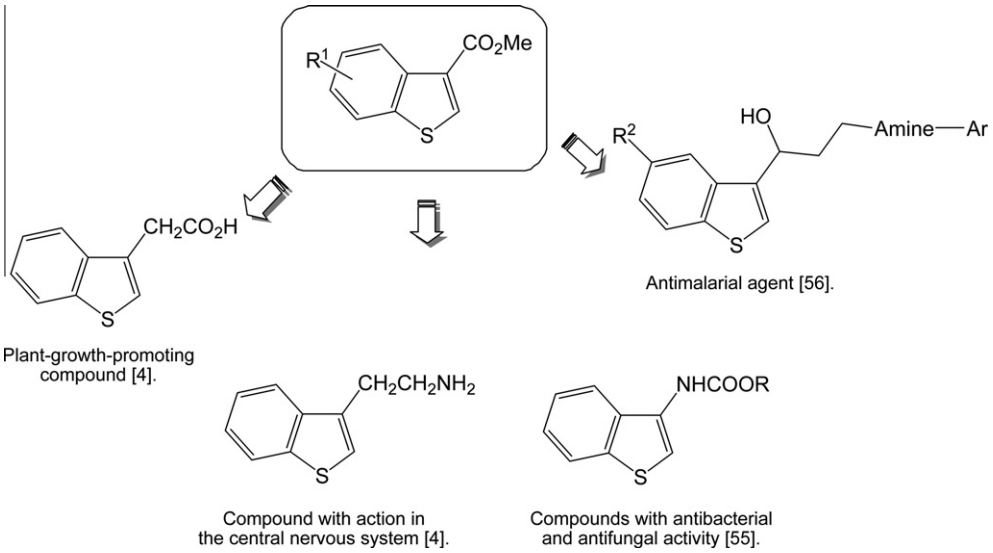


Fig. 3. Construction of simple benzo[*b*]thiophenes through functional group transformations on the expected DA reaction products. R^1 is any group coming from the diene. R^2 = F; Amine is piperazine and Ar is 1-naphthyl. R = alkyl, cycloalkyl, aryl.

As can be seen, the structural and electronic effects induced by the chemical substitution on the butadiene system produce different responses in the electrophilicity and nucleophilicity power. In fact, different trends are obtained regarding these two properties. For example, when analyzing the nucleophilicity index (Table 3), butadiene is suggested to be the poorest nucleophile as expected, whereas dieneamide **4.2** (N = 3.71 eV) is predicted to be a strong nucleophile when analyzing the nucleophilicity scale [18].

On the other hand, dienes **1**, **2** and **5** are predicted to be good nucleophiles using both scales (low ω value and high N value).

In order to characterize the nature of the DA reactions involving the dienophile **10**, the polarity of the process was assessed comparing the electrophilicity index of the diene/dienophile interacting pairs [40,60]. The marked differences in electrophilicity power between the thiophene derivative and the diene series (1.70–2.29 eV) indicate the polar character of these reactions. Moreover, for the pairs dienophile/Danishefsky's diene, dienophile/dieneamine and dienophile/Rawal's diene a higher regioselectivity is indicated ($\Delta\omega$ = 2.16, 2.24 and 2.29 eV, respectively, compared with 1.70–2.11 eV for the other dienes) [17a].

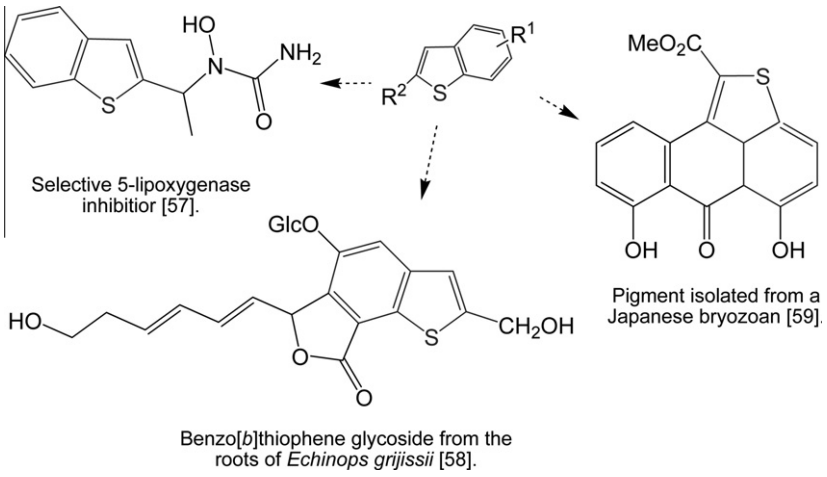


Fig. 4. Construction of complex benzo[*b*]thiophenes. R^1 is any group coming from the diene. $R^2 = CO_2Me$, CN, Br.

Table 3
B3LYP/6-31G(d). Global properties such as μ, η, ω and N are shown in eV and polarizability, in a.u.

Diene	μ	η	ω	N	$\langle\alpha\rangle$
5	−2.41	4.83	0.60	4.31	78.05
2	−2.36	5.08	0.55	4.22	164.79
1	−2.69	5.33	0.68	3.77	116.08
4.2[a]	−3.33	4.85	1.14	3.71	111.86
3	−2.79	5.33	0.73	3.67	101.16
4.1[a]	−3.01	4.80	0.94	3.59	112.47
Butadiene	−3.45	5.67	1.05	2.83	41.12

[a] Four conformations were analyzed for this dieneamide (Fig. 5). The pair of conformers in which the propyl substituent is at the same side of the conjugated system (i.e. 4.1 and 4.2) have the lowest relative energy (B3LYP/6-31G(d) + ZPE: ΔE = 0.96 kcal mol^{-1}). Therefore, these two conformers are considered thereafter.

3.2. Identification of reactive sites on the dienophile and dienes

To identify the most reactive site of the dienophile and dienes, the Fukui functions at C_2, C_3, C_4, and C_5 of the dienophile; and $C_{1'}$ and $C_{4'}$ of the dienes as well as local electrophilicity and nucleophilicity indexes derived therefrom, were evaluated [17a].

The results obtained from solvent calculations are gathered in Tables 4 and 5 (see Fig. 2 for atom numbering). The highest local electrophilicity (nucleophilicity) value for the dienophile (dienes) is in bold. The results for gas-phase calculations are included in Supplementary Material.

Different levels of theory were included based on preliminary studies concerning DA reactions between furan derivatives and Danishefsky's diene [61]. There it was found that only when the LANL2DZ basis set is used (at HF or B3LYP levels) and the solvent (benzene, CPCM) is considered in the calculations of regional Fukui functions, the local indexes account properly for the observed regioselectivity in all the analyzed cases.

Methyl 5-nitrothiophene-3-carboxylate (**10**) displays the highest electrophilic activation at C_4 for all levels of theory (Table 4). In contrast, analysis of the regional Fukui function for this dienophile in gas-phase reveals a different reactivity tendency depending on the basis set used (Table S1, Supplementary material).

All dienes show their maximum nucleophilicity value at the $C_{4'}$ site regardless of the media (gas phase/benzene) or the level of theory (Table 5, see also Tables S2–S4 of Supplementary material).

Hence, in the case of the thiophene derivative the preferred addition is to the nitro-substituted double bond. The nitro group, as a stronger electron-withdrawing moiety than the ester substituent, acts as a regiodirector orienting the DA reaction towards the double bond to which it is directly attached. As a result, the cycloadduct resulting from the C_4 (dienophile)–$C_{4'}$ (diene) interaction is expected to be formed.

Taking into consideration the large difference in the values of $N_{C1'}$ and $N_{C4'}$ for dienes **1** and **4** (Table 5), a good regiocontrol is likely for the DA reactions involving these dienes. However, due to the substitution pattern of both dienes, the expected products will have similar substituents in the same positions of the benzo[*b*]thiophene ring (i.e. CO_2Me at C_3 and OH at C_5 for the product originated with diene **1**, and CO_2Me at C_3 and OTBS at C_5 for the product of the reaction with diene **2**) [62]. Moreover, diene **2** has to be synthesized [63] whereas diene **1** is commercially available [31]. Therefore, for simplicity we chose Danishefsky's diene as an electron-rich component (Table 3) in order to continue with this investigation.

Several dieneamines were demonstrated to be unstable under thermal conditions when they were tested with a variety of dienophiles, preventing the DA reaction [64]. For this reason the

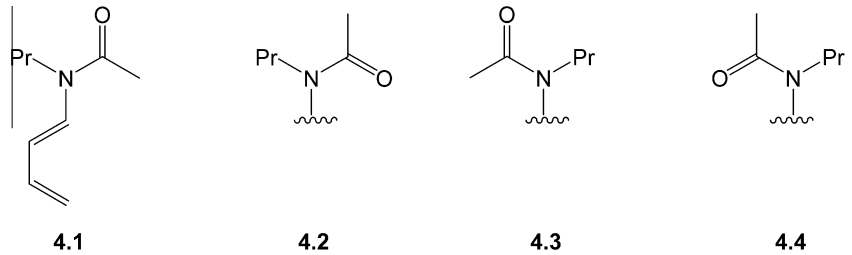


Fig. 5. Different conformers for the dieneamide 4. Relative energies (kcal mol^{-1}): ΔE (4.2) = 1.0 (gas-phase) and 0.6 (benzene), ΔE (4.3) = 2.4 (gas-phase) and 2.0 (benzene), ΔE (4.4) = 3.8 (gas-phase) and 3.3 (benzene).

Table 4
Local electrophilicity values for the dienophile (benzene, CPCM). Levels of theory: B3LYP/6-31G(d); B3LYP/LANL2DZ; HF/LANL2DZ.

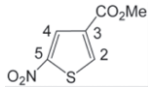
Molecule	Site k	ω_k (eV)
	2	0.42; 0.42; 0.23
	3	0.01; 0.00; 0.01
	4	**0.43**; **0.50**; **0.24**
10	5	0.11; 0.07; 0.06

Table 5
Local nucleophilicity values for dienes **1**–**5** (benzene, CPCM). Levels of theory: B3LYP/6-31G(d); B3LYP/LANL2DZ; HF/LANL2DZ.

Diene	Site k	N_k (eV)
1[61]	1′	0.51; 0.51; 0.66
	4′	**1.33**; **1.31**; **1.29**
2	1′	0.37; 0.33; 0.50
	4′	**1.07**; **1.08**; **1.18**
3	1′	0.73; 0.73; 0.88
	4′	**0.90**; **0.89**; **0.98**
4.1	1′	0.49; 0.49; 0.68
	4′	**0.78**; **0.77**; **0.87**
4.2	1′	0.56; 0.56; 0.75
	4′	**0.83**; **0.82**; **0.95**
5	1′	0.47; 0.43; 0.66
	4′	**1.00**; **1.01**; **1.10**

dieneamine **5** is discarded in spite of being an activated nucleophile (Table 3).

Finally, dienes **3** and **4** are chosen as moderately activated components towards polar DA reactions.

3.3. Mechanism of the DA reactions

The mechanistic aspects of the DA reactions that are initialized by the nucleophilic attack of $C_{4'}$ of the diene to C_4 of the dienophile will be considered in detail. For each reaction, two stereoisomeric channels are feasible (*endo* and *exo*, with respect to nitro). The possible modes of addition are depicted in Scheme 2 .

The calculations show that both TS are highly asymmetric (Δr_{endo} = 1.19 Å and Δr_{exo} = 1.03 Å for **3**; Δr_{endo} = 1.21 Å and Δr_{exo} = 1.07 Å for **4.1**; Δr_{endo} = 1.04 Å and Δr_{exo} = 0.99 Å for **4.2**; Δr_{endo} = 1.15 Å and Δr_{exo} = 1.22 Å for **1**) [65]. In all the cases, the formation of one of the new sigma bonds (i.e. $C_{4'}$ of the diene and C_4 of the dienophile) is more advanced because it involves the interaction between the most nucleophilic and electrophilic sites of the reactive pair diene/dienophile. The TS structures for both channels are shown in Fig. 6.

Domingo et al. suggested to denote reactions that proceed in a single kinetic step through highly asynchronous TSs as *two-stage one-step* mechanisms [66].

Calculated activation and reaction energies including ZPE corrections in benzene as solvent are summarized in Table 6 (ΔE_{act} and ΔE_{react}). The values at 433 K (the temperature used in the actual syntheses) are similar to those obtained at 298 K. In two cases (reactions with **3** and **4.2**) the *endo*-stereoisomer is preferentially formed (channel 1), being the activation energies lower than for the *exo*-addition. In contrast, with diene **4.1** the *exo* approach is favored over the *endo*. For the reaction with **1** a quite small difference is found between the *endo* and *exo* reaction barriers suggesting that both mechanisms could be operating in this case.

Except for the reaction between **10** and the dieneamide (i.e. **4.1** and **4.2**), the *exo*-cycloadducts are more stable than the *endo* products.

Generally, the effect of the solvent benzene as obtained by CPCM single-point calculations leads to a preferential stabilization of the reactants and transition states with a concomitant decrease of ΔE_{react} (Tables S5 and S6, Supplementary material).

On the other hand, an increase of the reaction barriers is observed when considering entropic corrections (Table 6, ΔG^{*}_{act}). It is also clear that the formation of all the cycloadducts is endergonic (Table 6, ΔG^{*}_{reac}). In spite of these main differences between ZPE corrected energies and Gibbs free energies, the general conclusion for each diene/dienophile pair is the same as the one obtained by analyzing the energetic data.

The incorporation of the corresponding thermal corrections increases the relative free energies (Table 6, ΔG^{*}_{act} and ΔG^{*}_{reac}, see the values in brackets). Moreover, the formation of all the cycloadducts is endergonic by 8–19 kcal mol^{-1} (Table 6, ΔG^{*}_{reac}, see the values in brackets). Nevertheless, the expected aromatization of the cycloadducts (i.e. HNO_2 elimination) should lead to considerably more stable products (see Section 3.4).

The reasons for the decrease in the Gibbs free energy barriers (i.e. $\Delta G^{*}_{10+1} < \Delta G^{*}_{10+4} < \Delta G^{*}_{10+3}$) when comparing the four favorable reactions (Table 6, in bold) may derive from the fact that diene **1** has the largest polarizability (Table 3) which favors the electronic transfer between the two partners (i.e. transfer of charge from donor diene to acceptor dienophile). Moreover, this diene has a convenient substitution pattern that cause a synergic increase in the nucleophilic character of $C_{4'}$ (Table 5) and a good nucleophilicity power (Table 3).

According to the observed trend in ΔG^{*}_{act} values, it is expected that the DA reaction between **10** and diene **1** is more favorable than with diene **3**. The formation of the cycloadduct generated by the reaction of **10** + **3** is kinetically very unfavorable.

As a complement of the theoretical study, in order to corroborate this predicted trend, we performed the corresponding thermal reactions. The experimental results are presented and discussed below.

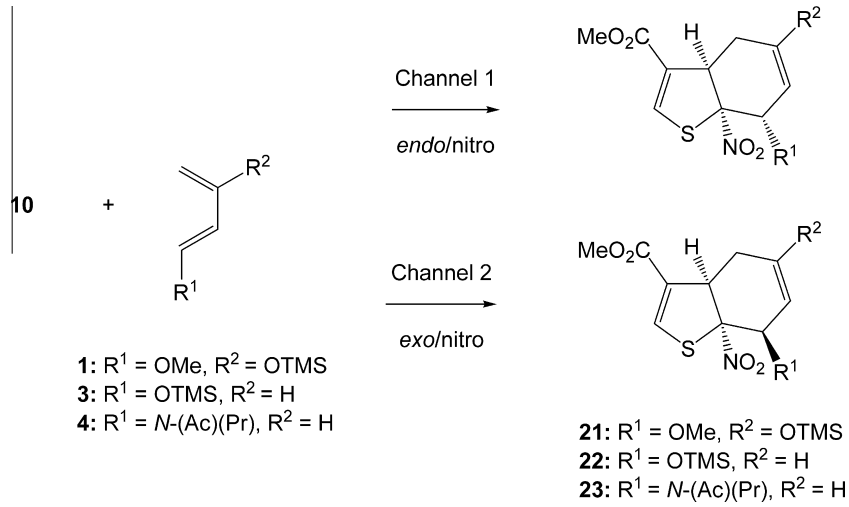
3.4. Experimental verification

In the three reactions studied here, **10** + **1**, **10** + **4**, and **10** + **3**, the attack by the diene occurs at the C_4–C_5 double bond of the thiophene ring in accordance with the results based on the local indexes. Thermal extrusion of the nitro group from the cycloadducts and the formation of aromatic products took place during the reaction time (Scheme 3). The isolation of the nitro-substituted cycloadduct could not be achieved under the reaction conditions used.

For the thermal reaction between **10** and **3**, only traces of the aromatic product **28** (i.e. methyl benzo[*b*]thiophene-3-carboxylate), which was originated from the DA cycloadduct, were experimentally detected by GC–MS of the reaction crude (Scheme 3).

On the other hand, diene **4** afforded a dihydrobenzo[*b*]thiophene derivative in very low yield. Based on the local indexes analysis, the expected product in this reaction is methyl 7-(*N*-propylacetamido)-4,7-dihydrobenzo[*b*]thiophene-3-carboxylate **26**. Traces of an aromatic compound originated from the DA cycloadduct (i.e. methyl benzo[*b*]thiophene-3-carboxylate **28**) were also detected by GC–MS of the reaction crude (Scheme 3).

Finally, according to the theoretical predictions described above, the DA reaction of **10** with the highly functionalized diene **1** gave the aromatic alcohol **27**, originated from the DA cycloadduct, in moderate yield (42%). In this case, the DA cycloadduct lost the nitro group as nitrous acid (**21** → **24**, Scheme 3) followed by hydrolysis of the silyl group and methanol elimination, giving the corresponding aromatic product during the reaction time (**24** → **27**, Scheme 3). A completely similar behavior was also



Scheme 2. Possible modes of addition that involve the participation of the reactive sites indicated by the local indexes in the DA process.

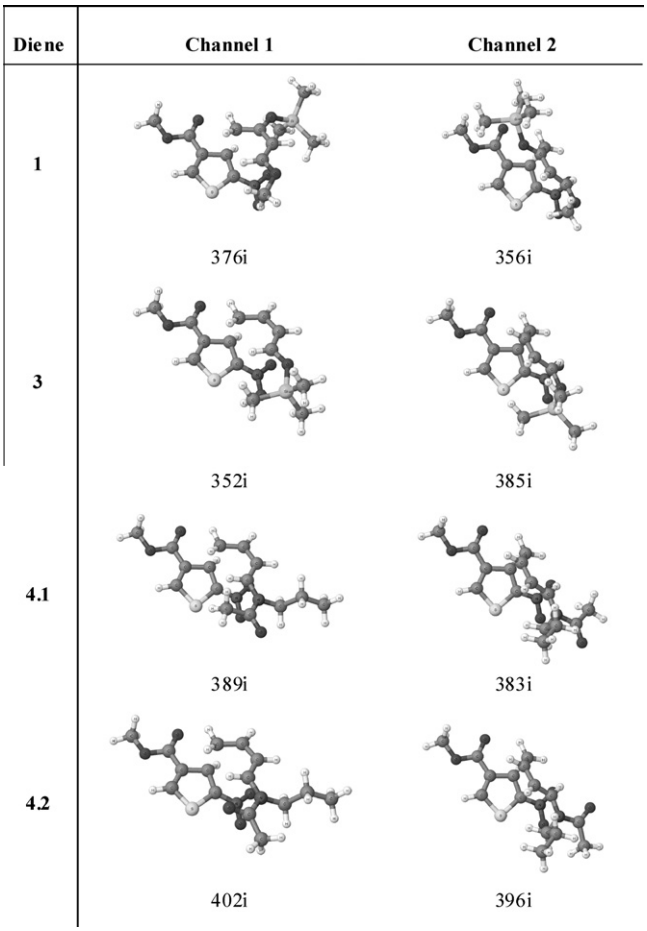


Fig. 6. Optimized TS structures.

observed in a variety of other DA reactions with the same diene [6a,6c,33,67].

For comparable DA reactions using nitropyrroles [6a], nitroselenophenes [6b] and nitrofurans [6c] with substituted 1,3-butadienes, it was experimentally demonstrated that the nitrated cycloadducts suffered *cis*-extrusion of the nitro group as nitrous acid and subsequent aromatization. Moreover, the mechanism for the reactions involving nitrofurans was fully characterized using

Table 6
Energetic and thermodynamic results at 298 K (433 K). B3LYP/6-31G(d), benzene, SP/CPCM. The data is organized in ascending order of ΔG^{*}_{act} values.

Diene	Mode	ΔE_{act}	ΔE_{reac}	ΔG^{*}_{act} [a]	ΔG^{*}_{reac} [a]
1	*Endo*	**15.5**	−9.1	**28.9** (**35.2**)	4.3 (10.8)
	Exo	**15.7**	−10.5	**28.9** (**35.1**)	2.4 (8.5)
4.1	*Endo*	20.1	−3.0	32.7 (38.3)	10.8 (17.4)
	Exo	**17.9**	−1.3	**30.3** (**36.2**)	12.2 (18.7)
4.2	*Endo*	**17.7**	−6.2	**30.7** (**36.8**)	7.5 (14.1)
	Exo	19.7	−4.1	32.4 (38.3)	9.4 (15.9)
3	*Endo*	**19.6**	−8.5	**32.1** (**38.0**)	4.4 (10.7)
	Exo	21.6	−10.5	33.9 (39.7)	3.4 (10.2)

[a] Standard state conversion from gas-phase to solution-phase for a DA reaction: $\Delta G^{*}_{i} = \Delta G^{o}_{i} - X$. The subscript *i* stands for *act* or *reac*; the superscript open circle indicates the use of a standard-state gas-phase pressure of 1 atm and the correction factor *X* is equal to 1.9 and 2.8 kcal mol^{-1} at 298 and 433 K, respectively.

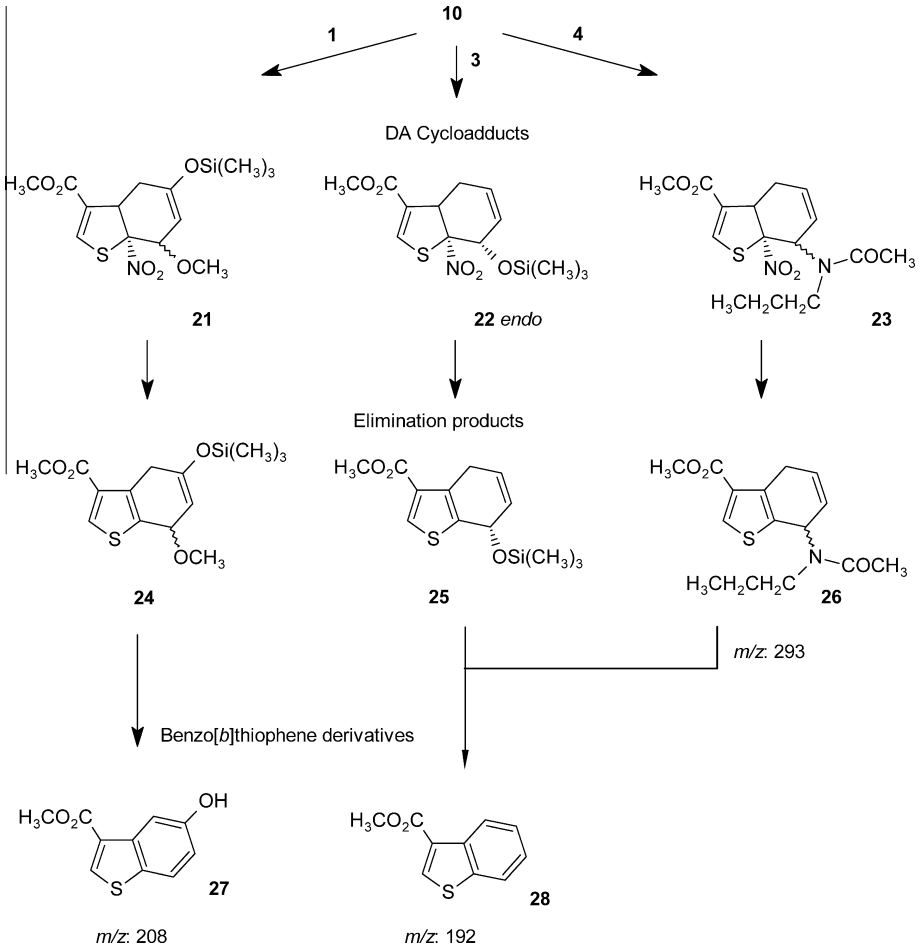
DFT methods and it was shown that the elimination step, leading to stable elimination products ($\Delta G^{*}_{reac} \sim -22$kcal mol^{-1} at B3LYP/6-31(G)d level, relative to the reactive pair), was the responsible factor for the feasibility of the overall process [68].

Therefore, in an analogous manner to the reactions involving nitropyrroles, nitroselenophenes and nitrofurans under thermal conditions, elimination of HNO_2 from the DA cycloadducts and conversion of the elimination products into benzo[*b*]thiophene derivatives contribute to the overall domino processes (Scheme 3) that are initialized by nucleophilic attacks of electron-rich dienes to the electron-deficient dienophiles in polar DA reactions, with *two-stage one-step* mechanisms [66].

For the reliable DA reaction to synthesize benzo[*b*]thiophene derivatives under thermal conditions (i.e. **10** and **1**), the reaction product was characterized (see experimental section) and the regiochemistry was elucidated. The obtained result is in agreement with the theoretical outcome (Scheme 3) that predicts the reaction to take place regiospecifically at the nitro substituted C=C double bond.

As shown in Fig. 3, the benzo[*b*]thiophene system could be subsequently manipulated, thus extending its utility in synthesis. Moreover, the ester is a versatile unit because of the large variety of chemical transformations it allows on the reaction products.

The tendency concerning the ΔG^{*}_{act} values that was established previously (Table 6) is in agreement with the experimental results shown here (i.e. the highest yield was obtained for the reaction which was calculated to be kinetically favored and only traces of the product were detected in the kinetically disfavored reaction).



Scheme 3. These results are based on DFT computations and experimental work.

3.5. Summary of methodology

We showed how DFT methods can help in the work of synthetic organic chemists in order to plan a certain reaction (polar DA reaction in this case) considering a variety of available reagents. The suggested procedure consists of the following steps:

(1) Analyze the global DFT-based indexes (i.e. ω and N) taking into consideration that the reaction feasibility depends on the electrophilic and nucleophilic character of the reacting pairs. The best combinations are between strong electrophiles and strong nucleophiles.
(2) Pre-select the most promising electrophile/nucleophile pairs and analyze the local DFT-based indexes (i.e. ω_k and N_k) in order to predict the regiochemistry of the cycloadduct. Here it will be possible to discard the reagents that do not provide the required regioisomer.
(3) Once the potential reactive pairs are selected (at this point the list of reagents is probable more reduced than the initial one), a final selection can be done by using thermodynamic criterions based on TS computations (i.e. the reactions with the lowest ΔG^{*}_{act} values are preferred in this step).
(4) The last part consists of carrying out the reactions that were indicated to be promising in the previous step.

This methodology is not only limited to the rational selection of reacting pairs in polar DA reactions, it can also be used to explain experimental tendencies and get insights into the reaction mechanisms.

4. Conclusion

A variety of synthetically and commercially available nitrothiophenes were proposed as strong electrophiles in order to participate in polar DA reactions. The series was analyzed in detail with the aim of selecting a potential dienophilic candidate.

The reactive counterparts which consist of a variety of dienes substituted with electron-releasing groups were also investigated using DFT-based indexes.

The feasibility of methyl 5-nitrothiophene-3-carboxylate (**10**) to act as electrophile in polar DA reactions towards the electron-rich dienes **1**, **3** and **4** was established using the TS framework and corroborated in an experimental way.

The global properties of the diene/dienophile pairs illustrate the polar character of the DA reactions.

It was found that the attack of the dienes should take place at the nitro substituted double bond of the dienophile to give the DA cycloadducts. The use of a high nucleophilically activated diene and an electron-deficient dienophile (i.e. **1** and **10**) should allow the reaction to proceed with a total regiocontrol, as indicated by the local nucleophilicity index and the difference in electrophilicity power.

Danishefsky's diene (**1**) is indicated to be the most reactive diene of the series, being the feasibility of the polar reaction with **10** the most favorable. In a kinetically controlled reaction this cycloaddition should proceed through both channels (i.e. *endo* and *exo*) because there is no difference between the barriers associated to the cycloadduct formation in benzene at 433 K. The reaction mechanism is *two-stage one-step* which proceeds through a highly asynchronous TS.

All the computational predictions are in good agreement with the experimental results.

Acknowledgments

R. Brasca thanks the European Commission for the Erasmus Mundus External Cooperation Window (EMECW) Lot 16 Scholarship and CONICET for the Doctoral Grant Programme.

We thank Dr. M.A. Romero (Instituto de Desarrollo Tecnológico para la Industria Química, CONICET) for his help in computations.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2011.11.050.

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