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Improvements in Diels–Alder cycloadditions with some acetylenic compounds under solvent-free microwave-assisted conditions: experimental results and theoretical approaches

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Abstract—The Diels–Alder irreversible cycloadditions of 1,3-cyclohexadiene **1**, 3-carbomethoxy-2-pyrone **2** and 2-methoxythiophene **3** with acetylenic dienophiles under solvent-free conditions are described. By strict comparisons with conventional heating under similar conditions, important specific microwave effects are revealed in the two last cases whereas they are absent in the first one. They are discussed in terms of asynchronous mechanisms in agreement with ab initio calculations at the HF/6-31G(d) level indicating dissymmetries in transition states. Specific MW effects can be understood by considering the enhancements in dipole moments from ground states to transition states.
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1. Introduction

Coupling solvent-free reactions and microwave (MW) activation allows numerous improvements in organic synthesis.[1–7] Acceleration of chemical reactions under MW radiation can result from either thermal effects due to wave–materials interactions resulting in a rapid and homogeneous raising in temperature, or (and) specific non-purely thermal effects.[4,6,7] These last ones can be connected to organization of polar systems when submitted to an electromagnetic field, leading to decreases in the activation energy[8,9] or increases in the pre-exponential factor in Arrhenius law[10–12] or to microscopic hot spots[13–15] as for instance advocated in sonochemistry.[8]

Among the most popular reactions in organic synthesis, Diels–Alder cycloadditions were currently studied under MW irradiation.[16] Only few strict comparisons between MW and conventional heating (△) under similar sets of conditions are available and describe rather contradictory conclusions.

The possible intervention of specific MW effects is clearly dependent on reaction medium, substrates and mechanisms.[4] With nearly-symmetrical reagents, no or weak MW effects are involved,[16f,g] whereas they are clearly important with a lot of non-symmetrical hetero Diels–Alder reactions[16b,h–1] where often reactions only occurred under MW.

To put into evidence such possible MW effects, one needs a strict comparison of reactions under MW activation or with conventional heating (△) using an oil bath under the similar sets of conditions (time, temperature, pressure…). To this purpose, the Synthewave® 402 reactor from Prolabo operating with focused waves (monomode system)[1] is especially convenient. It allows mechanical stirring of the reaction mixture, the measurement of temperature by infrared detection,[17] its modulation according to emitted power to maintain the temperature constant and a monitoring of profiles of raising in temperature.

Non-catalyzed Diels–Alder cycloadditions are especially suitable cases to be considered under MW activation in solvent-free conditions since they need classically extended heating times in refluxing solvents. To draw unambiguous conclusions on MW activation, further studies need preferably to avoid any thermodynamical equilibrium by retro Diels–Alder reversibility. To this purpose, we consider here some examples of Diels–Alder cycloadditions of different dienes **1**–**3** with activated acetylenic dienophiles. The reactions are irreversible in nature due to expulsion of light small molecules from adducts

($H_2C=CH_2$, CO_2, elemental S) allowing aromatization (Eqs. 1–3). To the best of our knowledge, only one parent case was studied concerning MW enhanced reactions of 1,3-cyclohexadienes and acetylenic compounds but unfortunately without any control blank experiments by conventional heating under similar conditions.[18]

MW reactor. As the vessel is only irradiated in the bottom part, its upper part behaves as a cold wall to avoid removal of the dienophile.

In spite of the absence of any MW specific effects (entries 2/3 and 4/5), the solvent-free procedure constitutes here an

(1)

(2)

(3)
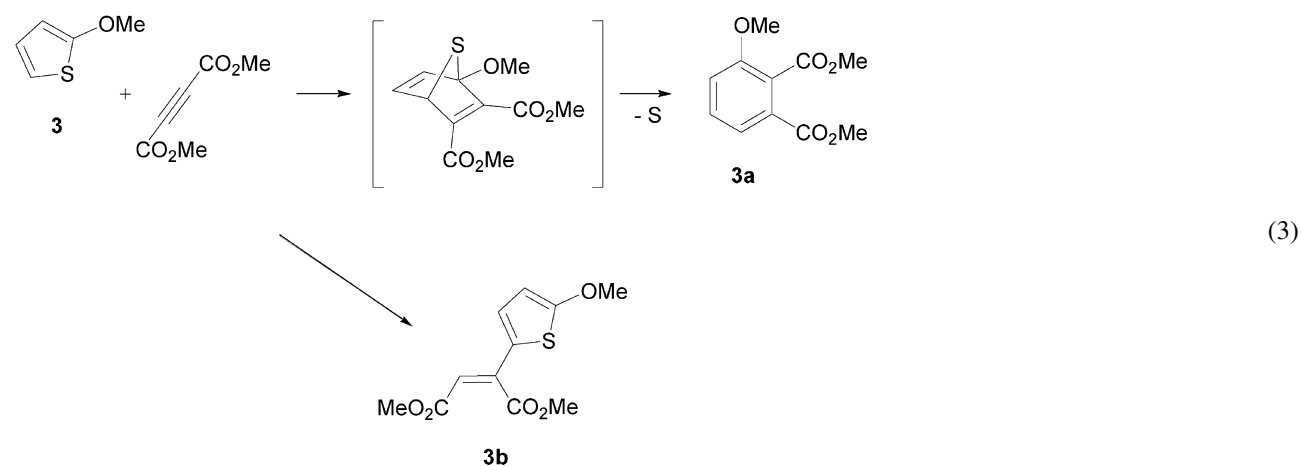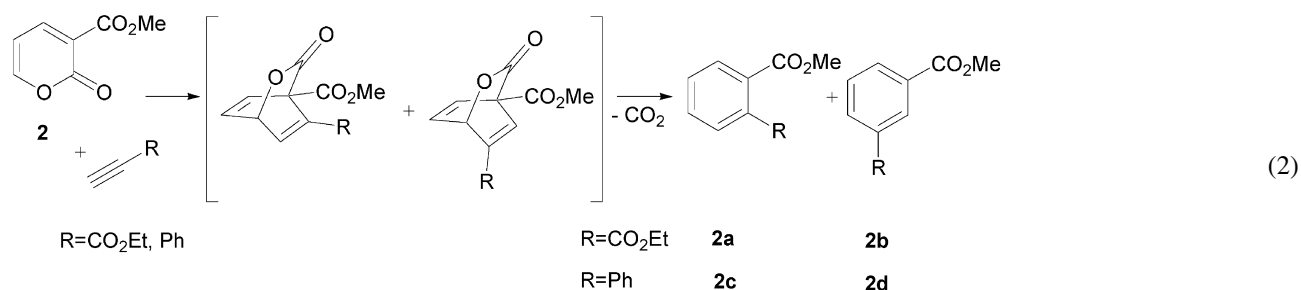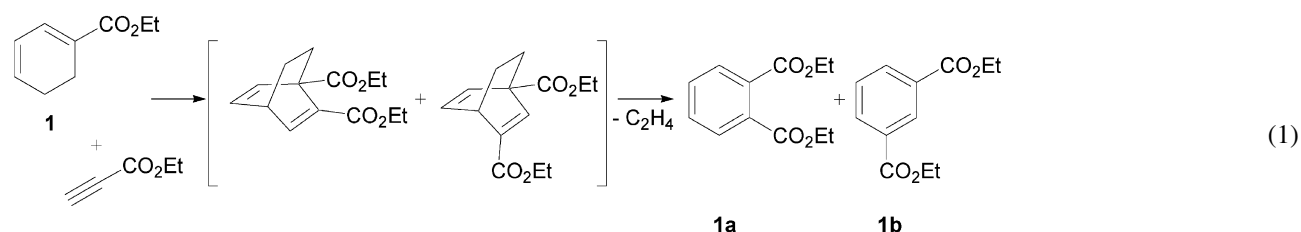
2. Results

2.1. Reaction of ethyl 1,3-cyclohexadiene carboxylate 1 with ethyl propiolate (EP) (Eq. 1)

In the literature,[19] this reaction was described under very harsh conditions (benzene at 320 °C within 24 h) with a very poor yield (17%) and no selectivity (**1a/1b**=50:50).

When realized either in the absence of solvent or on silica gel as a support in 'dry media' the reaction could be performed at 150 °C (Table 1). Taking into account the boiling point of ethyl propiolate (120 °C), the open system can be used with a rather long tube (roughly 8 cm) inside the

undeniable improvement for the reaction (no solvent, atmospheric pressure, shorter reaction times and lower temperatures) with enhanced yields from 17 to 36–37% (entries 2, 3, and 5).

2.2. Reaction of 3-carbomethoxy-2-pyrone 2 with ethyl propiolate or phenyl acetylene (Eq. 2)

Reaction of pyrone **2** with ethyl propiolate was reported by Reed and coll.[20] to occur for 30 h in refluxing xylene with a yield of 50% (**2a/2b**=20:80). With phenyl acetylene as the dienophile, a 60% yield was obtained with a poor selectivity (**2c/2d**=65:35) by extended heating in toluene at 250 °C (in closed vessels) for 24 h. This same experiment was also

Table 1. Reaction of **1** (0.20 g, 1.31 mmol) with ethyl propiolate (0.26 g, 2.63 mmol) at 150 °C under microwave (MW) irradiation or conventional heating (△)

Entry	Activation	Medium	Temperature (°C)	Time (h)	Yield (%)[a] **1a+1b**	**1a/1b**[a]
1	△[19]	Benzene	320	24	17	50:50
2	△	No solvent	150	2.5	36	53:47
3	MW	No solvent	150	2.5	37	52:48
4	△	Silica gel[b]	150	1	25	60:40
5	MW	silica gel[b]	150	1	36	60:40

[a] GC yields and ratios using an internal standard (ethyl diethylmalonate).
[b] 1 g of support for 0.20 g of **1**.

described in xylene at 200 °C for 24 h with a non-specified yield and a conversion of 97% without any subsequent purification.[21]

In our hands, reactions were, therefore, performed either in xylene or solvent-free conditions at atmospheric pressure under microwave or traditional heating for the same times and temperatures (Table 2).

Thanks to important specific MW effects, results obtained under solvent-free conditions (entries 9 and 13) are by far better than the ones previously published under classical conditions (entries 6 and 10) within short reaction times and easier procedures. For instance, with ethyl propiolate, the yield of 80% within 2 h at 120 °C under solvent-free MW assisted conditions constitutes a noticeable improvement to the classical reaction in xylene for 30 h (50%). On another hand, with phenyl acetylene, the yield is equivalent using solvent-free conditions and MW activation within 3 h at 150 °C when compared to the one day procedure in toluene at 250 °C.

In both cases, very important kinetic specific MW effects are evidenced (entries 8/9 and 11/13).

Dealing with selectivity, it appears to be significantly improved by this method in the case of phenyl acetylene since only the regioisomer **2c** is obtained (no traces of **2d** were detectable by GC or NMR). Selectivity is only slightly modified in the case of ethyl propiolate (entries 8 and 9) from **2a/2b**=42:58 (△) to 31:69 (MW).

2.3. Reaction of 2-methoxythiophene 3 with dimethyl-acetylenedicarboxylate (DMAD) (Eq. 3)

According to literature,[22] the progress of this reaction is deeply affected by the nature of the medium. When performed in refluxing xylene, it leads to Diels–Alder cycloaddition (96 h) whereas, when carried out in acetic

acid at 100 °C, Michael addition is observed (8 h). In both cases, yields remained very poor (**3a**: 17% and **3b**: 28%, respectively). This reaction was thus performed in xylene, in solvent-free conditions and in acetic acid either under MW activation or in a thermostated oil bath under similar conditions (Table 3).

Serious improvements in yields and experimental conditions are evidenced in both cases when one consider the yields of 65% (entry 20) and 49% (entry 23) obtained, respectively, for **3a** and **3b** when compared to those of 17 and 28% reported in the literature.

It is noticeable that the Michael product consists in a single isomer **3b**. The *E* configuration was confirmed by assignment on the basis of the chemical shifts using NOESY 1D experiment. Irradiation of ethylenic proton at 5.92 ppm increased intensity of proton doublet at 6.86 ppm.

In both cases, important specific MW effects when compared to classical heating are revealed. If this effect seems rather limited for Diels–Alder cycloadditions (MW: 65%, △: 40%), it is much more significant for Michael addition (MW: 49%, △: 4%). Furthermore, the competition between the two processes is highly affected by the mode of activation. Every conditions being equal elsewhere, Michael addition is favored under MW when compared to conventional heating (**3a/3b** is enhanced from 60:40 to 17:83, entries 22/23).

3. Discussion

3.1. Comparisons with literature

Solvent-free conditions lead by far to serious improvements, which can be due to some extent to enhancement in concentration of reagents. They are conducted under easy-to-perform techniques involved in Green Chemistry:

Table 2. Reaction of **2** (0.50 g, 3.25 mmol) with acetylenic compounds (0.45 and 0.46 g, 4.55 mmol) under MW irradiation or conventional heating (△)

Entry	R	Activation	Medium	Temperature (°C)	Time (h)	Yield (%)[a,b]	Products[a,c]
6	CO₂Et	△[20]	Xylene	140	30	50	**2a/2b**=20:80
7		MW	Xylene (3 ml)	120	2	7	**2a/2b**=28:72
8		△	No solvent	120	24	19 (19)	**2a/2b**=(42:58)
9		MW	No solvent	120	2	80 (75)	**2a/2b**=(31:69)
10	Ph	△[20]	Toluene	250	24	60	**2c/2d**=65:35
11		△	No solvent	150	3	19	**2c**
12		△	No solvent	150	24	44 (40)	**2c**
13		MW	No solvent	150	3	64 (62)	**2c**

[a] GC yields and ratios using an internal standard (propyl phtalate when R=CO₂Et and diethyl phtalate when R=Ph).
[b] Yields of isolated products are reported in brackets.
[c] Ratios **2a/2b** and **2c/2d** have been determined by GC and ¹H NMR.

Table 3. Reaction of **3** (0.80 g, 7.02 mmol) with several amounts of DMAD in xylene (1 mL), or without solvent or in acetic acid (15 mL) under MW irradiation or conventional heating (△)

Entry	Activation	Solvent	3/DMAD	Temperature (°C)	Time (h)	Yield (%)[a,b]	
						3a	**3b**
14	△[22]	Xylene	1:3	140	96	17	—
15	△	Xylene	1:5	140	2	35	8
16	MW	Xylene	1:5	140	2	50	9
17	△	No	1:3	140	2	21	<2
18	MW	No	1:3	140	2	49	<2
19	△	No	1:5	140	2	40	7
20	MW	No	1:5	140	2	65 (64)	6
21	△[22]	AcOH	1:3	100	8	—[c]	28
22	△	AcOH	1:3	100	2	6	4
23	MW	AcOH	1:3	100	2	10	49 (48)

[a] GC yields using an internal standard (ethyl benzoate).
[b] Yields of isolated products are reported in brackets.
[c] Not reported.

In the first case (Eq. 1), we obtained a yield of 36% either under MW or thermal activations (entries 2 and 3) within 2.5 h in the absence of solvent under atmospheric pressure at 150 °C instead of lower yield (17%) within 24 h in benzene in closed vessels at 320 °C.

In the absence of solvent, the reaction of pyrone **2** (Eq. 2) was now improved up to 80% with ethyl propiolate within 2 h at 120 °C (entry 9) when compared to 50% in refluxing xylene and to 64% with phenyl acetylene (entry 13) within 3 h at 150 °C instead of 60% after 24 h in toluene in closed vessels under pressure at 250 °C.

In the last case (Eq. 3), in the absence of solvent, the yield in cycloadduct is improved up to 65% (entry 20) within 2 h at 140 °C when compared to 17% in refluxing xylene for 96 h. In acetic acid, the Michael adduct is obtained with 49% yield under MW for 2 h at 100 °C (entry 23) instead of 28% after 8 h by conventional heating.

From selectivity point of view, it is noteworthy that:

(i)   with cyclohexadiene **1**, the ratios **1a/1b** are nearly identical around 50:50 whatever the conditions examined in the absence or presence of solvent or silica gel and the selectivity remains rather identical;
(ii) with pyrone **2** and ethyl propiolate, the ratios **2a/2b** are slightly affected according to reaction conditions from 20:80 to 42:58 when comparing reactions in xylene and under solvent-free conditions. A slight modification of selectivity is also observed in the absence of solvent under classical heating and under MW (31:69). The most important change lies in the case of reaction **2** with phenyl acetylene as under solvent-free conditions the compound **2c** was obtained specifically instead of a mixture of **2c** and **2d** (65:35) in toluene;
(iii) with thiophene **3**, either in xylene or in dry media, Diels–Alder product **3a** is highly predominant versus Michael adduct **3b**.

We have to quote that, in all these cases, the regioselectivities were not especially affected by MW activation and remained rather the identical as under conventional heating.

On the contrary, in the case of reaction of **3** in acetic acid, the regioselectivity **3a/3b** is strongly affected by the mode of activation, starting from 60:40 by conventional heating up to 17:83 by MW under similar sets if conditions (2 h at 100 °C, entries 22 and 23).

3.2. Specific MW effects

The specific MW effects should be the reflect of the modification of polarity during the reaction progress from the ground state (GS) towards the transition state (TS).[4] If there is no development of charges in TS, in an isopolar mechanism, polarity remains unchanged and MW effect will be nil. On the contrary, if charges are developed in asynchronous TS, MW effect should be expected. Such an assumption, connected to the (a)synchronous character of the mechanism, was advanced recently by Cossio, Langa and coll.[23] when considering calculations for cycloadditions predicting asynchronous transition structures in cases where specific MW effects were evidenced and stating that the modifications are related to the relative energies and hardness of the transition structures involved.

It is noteworthy that, during the reactions of pyrone **2** and thiophene **3**, important specific MW effects are involved whereas they are absent in the case of cyclohexadiene **1**.

This important observation could be due to the fact that, in the cases of reactions depicted in Eqs. 2 and 3 under solvent-free conditions, these reactions occurred via asynchronous transition states. On the opposite, the absence of MW effects in case 1 could reflect a synchronous transition state. One can thus state that the possible MW effect should be an experimental indicator of synchronous or asynchronous transition state on the same way as differences in rates did.[24]

3.3. Theoretical calculations

Theoretical approaches can allow justifying these assumptions. Ab initio calculations were carried out at the Hartree–Fock level (HF/6-31G(d)) and Density Functional Theory (B3LYP/6-31G(d)) levels with several aims:

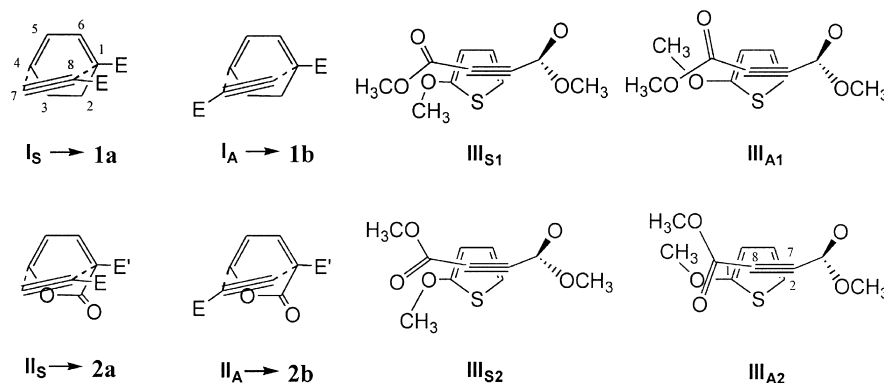1. optimization of TS geometries to assess the

Figure 1. Reagent approaches in reactions depicted in equations 1–3 (E=CO$_2$Et, E'=CO$_2$Me).

(a) synchronicity of the mechanism by comparing the relative degrees of the two bonds formation;
2. estimation of activation energies;
3. evaluation of dipole moments in GS and TS as a picture of enhancement in polarity during the reaction progress;
4. orbital frontier analysis to foresee relative reactivities.

3.4. Optimization of transition state geometries and evaluation of activation energies

In the cases of Eqs. 1 and 2 concerning cyclohexadiene **1** and pyrone **2**, two possible approaches were considered where the two esters groups are either *syn* (respectively, **I$_S$** and **II$_S$** for **1** and **2**) or *anti* (respectively, **I$_A$** and **II$_A$**) (Fig. 1). In the case of thiophene reaction with DMAD, four possible approaches were considered where the methoxy group of thiophene is either in *syn* or in *anti* conformation (respectively, **III$_S$** and **III$_A$**) and one carbonyl group in parallel plane is oriented on the same side of *syn* or *anti* methoxythiophene (respectively, **III$_{S2}$** and **III$_{A2}$**) or the contrary (respectively, **III$_{S1}$** and **III$_{A1}$**).

Theoretical calculations were carried out to evaluate the structures of the transition states corresponding to these different approaches and to determine the activation energy. The main results of calculations after full optimizations at HF/6-31G(d) level are indicated in Table 4. The values of activation energies were calculated at the DFT level [B3LYP/6-31G(d)] which allows to take into account the correlation effect (see Section 5.1).

From this Table, one can draw a lot of conclusions:

In case **I**, the two types of attack lead to rather close values of ΔE, justifying thus the poor selectivity observed (from 50:50 to 60:40 according to reaction medium).

In case **II**, *anti* attack is more largely preferred to *syn* approach by 2.1 kcal mol^{-1}, presumably due to less steric repulsion between the two esters groups. This difference can allow thus an improved selectivity favoring preferential access to **2b**, what is effectively observed with a selectivity of 80:20 in favour of **2b**.

The dissymmetry in TS, when considering the differences in lengths between linking bonds (Δd), is enhanced according to the sequence **III$_A$>II$_A$>I$_A$**. Therefore, the asynchronicity in reactions of thiophene **3** and then pyrone **2** is much more higher than in the case of cyclohexadiene **1**. This prevision is in good agreement with the magnitude of specific MW effects as we observed.

3.5. Case of reaction of pyrone 2 with phenyl acetylene

This case is especially interesting as leading to a single isomer **2c**. Ab initio calculations were performed at the HF/6-31G(d) level for the two possible optimized approaches *syn* and *anti* (Fig. 2).

It was evaluated that *syn* approach is largely preferred to *anti* approach by 5.6 kcal mol^{-1}. We can notice that this high value is perhaps amplified by the possibility of π-stacking between aromatic ring and ester moiety, this phenomenon intervenes at distances 3.5–5 Å[25] and is especially important in solvent-free medium.[26] We can therefore predict the formation of only one isomer (**2c**) resulting from *syn* approach.

Table 4. Distances between linking bonds and energies of activation for the attacks in Figure 1

	$d_{1,8}$ (Å)	$d_{4,7}$ (Å)	Δd (Å)	$\Delta E^{\#}$ (kcal mol^{-1})
I$_S$	2.300	2.055	0.245	20.7
I$_A$	2.162	2.261	−0.099	21.5
II$_S$	2.376	2.034	0.342	24.4
II$_A$	2.298	2.085	0.213	22.3
III$_{S1}$	3.093	1.971	1.122	21.1
III$_{S2}$	2.889	1.946	0.943	20.8
III$_{A1}$	3.142	1.955	1.187	20.4
III$_{A2}$	3.170	1.960	1.210	21.2

syn approach → **2c**
$\Delta E^{\#}$ = 21.9 kcal.mol^{-1}

anti approach → **2d**
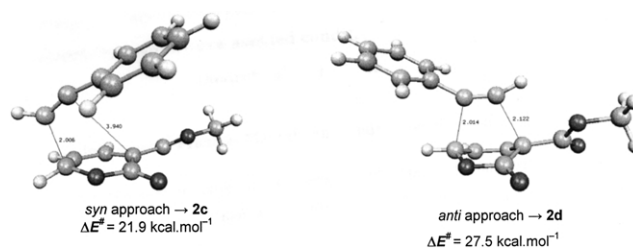$\Delta E^{\#}$ = 27.5 kcal.mol^{-1}

Figure 2. Transition states for the reaction of **2** with phenyl acetylene.

We can also notice the high dissymmetry in the TS (difference in bond lengths between linking atoms $\Delta d=1.934$ Å), justifying thus the high degree of asynchronicity for the mechanism and consequently the important MW specific effect.

3.6. Evolution of dipole moments from ground state to transition state

The same calculations as above give access to the values of the dipole moments. We give in Table 5 all of them for starting materials and the different TS. We have to notice the non-nil value for DMAD, which results from the position of the two esters moieties in two perpendicular planes.

In the cases of reactions 2 and 3, large enhancements in dipole moments from GS to TS are foreseen and could consequently give an explanation for the most important MW effects in these cases.

3.7. Frontier orbitals analysis of reagents

Usually in this type of reactions it is possible to justify relative reactivities and selectivities by considering the orbital frontier interactions. So, in Table 6, we indicate the energy levels of the orbitals concerned in the procedures.

The main frontier orbital interactions concern the HOMO of **D** and the LUMO of **E**. The sequence of reactivities connected to these interactions is **3>1>2**, which differ from the experimental one, i.e., **3>2>1**. The origin of the discrepancy can be explained as follow: due to the low energy LUMO level of **2**, it is necessary to take into account of the HOMO(**E**)/LUMO(**D**) interaction which can be added to the previous one.

3.8. Case of reaction of thiophene 3: Diels–Alder cycloaddition and Michael addition

In Eq. 4 are represented the two possible pathways (Diels–Alder and Michael reactions) when reacting thiophene **3** with **DMAD** according to reaction conditions leading to, respectively, **3a** and **3b**.
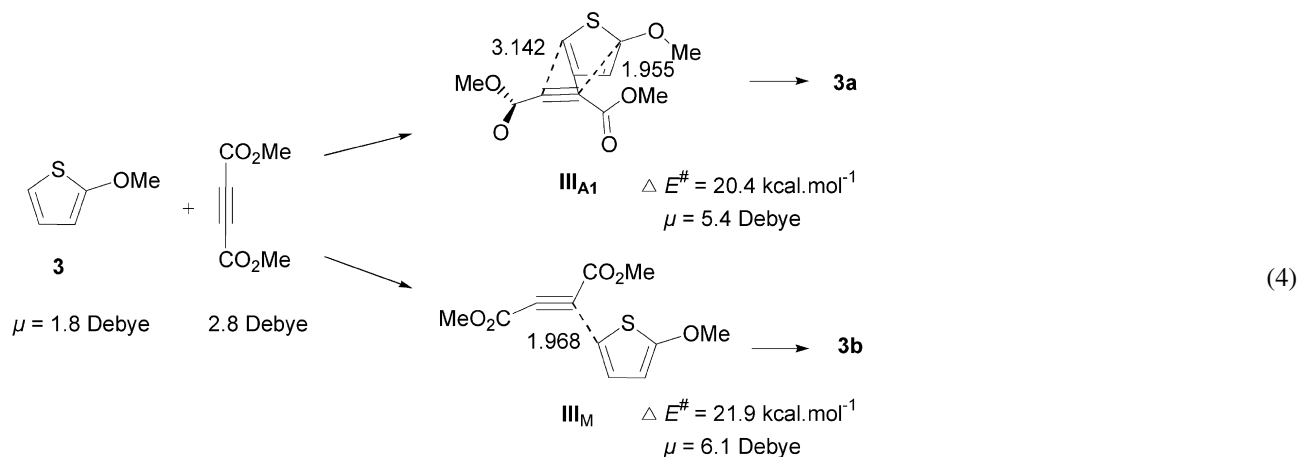
Table 5. Dipole moments of reagents and transition states carried out by HF/6-31G(d) level

	Ground states		Transition states	
Reaction Eq. 1	**EP**	**1**	**I$_S$**	**I$_A$**
μ (Debye)	2.2	2.4	0.4	1.9
Reaction Eq. 2	**EP**	**2**	**II$_S$**	**II$_A$**
μ (Debye)	2.2	3.3	4.8	5.2
Reaction Eq. 3	**DMAD**	**3**	**III$_{S1}$, III$_{S2}$**	**III$_{A1}$, III$_{A2}$**
μ (Debye)	2.8	1.8	5.83, 5.15	5.40, 8.02

When considering the differences in lengths between the newly formed bonds (1.8 and 2.7 cf. Δd in Table 4), an asynchronous mechanism has to be postulated for the Diels–Alder reaction. It could be certainly the reason why this special Diels–Alder cycloaddition is strongly favored under MW conditions when performed in an aprotic solvent or without solvent. The calculations of the relative activation energies $\Delta E^{\#}$ are clearly in agreement with experiments as, respectively, 20.4 and 21.9 kcal mol^{-1} for Diels–Alder (via the approach **III$_{A1}$**) and Michael reactions.

When one considers the relative dipole moments of the transition states, the polarity of **III$_M$** is higher than for **III$_{A1}$**. Consequently, under MW activation, one can expect an enhancement in Michael addition more important than for Diels–Alder, affecting thus the selectivity in favour of the first one.

In the case of pyrrole, a two steps mechanism has been considered.[27] The Michael addition intermediate should give the cycloaddition in aprotic systems while when a proton transfer is possible the Michael Addition product is observed.

The most important factor affecting the selectivity can be the solvent (xylene and no solvent gives the cycloaddition reaction while acetic acid gives the Michael addition product). We can expect that a protic solvent stabilizes better the more polar transition state, strengthening thus the tendency yet revealed in its absence (the solvent is not included in the calculation).

$$\mathbf{III_{A1}} \quad \triangle E^{\#} = 20.4 \text{ kcal.mol}^{-1} \quad \mu = 5.4 \text{ Debye}$$

$$\mathbf{III_M} \quad \triangle E^{\#} = 21.9 \text{ kcal.mol}^{-1} \quad \mu = 6.1 \text{ Debye}$$

(4)

Table 6. Energy levels of HOMO and LUMO orbitals of the reagents in atomic unities (hartrees)

Compounds		HOMO	LUMO	$\triangle(HOMO_D-LUMO_E)$	$\triangle(HOMO_E-LUMO_D)$
Dienes (D)	**1**	−0.31313	0.09501	0.43623[a]	0.51301[a]
	2	−0.34519	0.06258	0.46829[a]	0.48058[a]
	3	−0.31746	0.14313	0.43096[b]	0.57076[b]
Dienophiles (E)	**EP**	−0.41800	0.12310		
	DMAD	−0.42763	0.11350		

[a] E=EP.
[b] E=DMAD.

Also interesting in the same field is the result observed by Kaishnaiah and Narsaiah[28] who obtained Michael adducts during the reaction of pyridone **4** with DMAD under MW irradiation when carried out on neutral alumina under solvent free conditions instead of the expected Diels–Alder compounds (Eq. 5). Unfortunately, this same experiment was not studied under conventional heating.

(5)
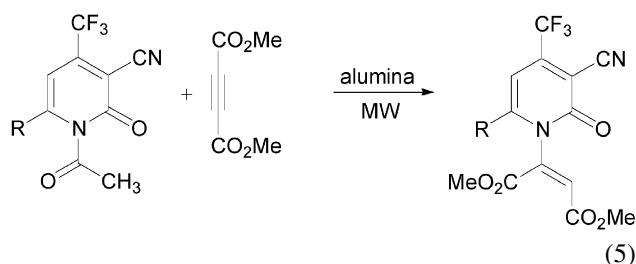
As a coherent interpretation, one can assume that alumina can interact specifically by hydrogen bonding with carbonyl groups from esters moieties as well as acetic acid.

4. Conclusion

Three cases of irreversible Diels–Alder reactions were considered with great success. Solvent-free conditions lead by far to the best results and to easy-to-perform procedures with considerable improvements over classical methods. MW effects are very favorable in the cases of reaction of pyrone **2** and thiophene **3**. The observed specific MW effect is according to the sequence **1**<**3**<**2**, what could be understood by considering the concerted character of the mechanism: **1** may react via a totally concerted mechanism and **2** and **3** via polar non symmetrical ones involving development of charges. All the observations were supported by ab initio calculations taking into account the activation energies, the dissymmetry in TS geometries and enhancements of dipole moment from GS to TS.

In the case of thiophene **3**, an important change in selectivity (competitive Diels–Alder vs Michael reactions) is observed in acetic acid. Under the same conditions, MW strongly favored the Michael addition versus Diels–Alder reaction when compared to conventional heating, presumably via the more polar mechanism. This point could be supported by an increase in the dipole moment from GS to TS in the case of Michael addition. However, the solvent can also certainly contribute to the change in reactivity and selectivity.

5. Experimental

Ethyl 1,3-cyclohexadiene carboxylate **1** was prepared according to a new MW-assisted procedure as an improved and efficient method when compared to classical ones.[29] Pyrone **2**, thiophene **3** and all the dipolarophiles (ethyl propiolate, phenyl acetylene and DMAD) are commercially available.

Reactions were performed by mixing dienes **1**–**3** with dipolarophile in the relative amounts indicated in the Tables 1–3 in a Pyrex tube, which was submitted to MW irradiation in a monomode reactor Synthewave® S402 from Prolabo[1] at temperatures and for reaction times indicated in the Tables. At the end of the reaction, when reactions were carried out up to full conversion of dienes (followed by TLC on Merck silica gel 60 F_{254} plates, using UV light at 254 nm and methylene chloride for detection), the mixture was cooled to room temperature and dissolved in methylene chloride. Crude products were analyzed by capillary gas chromatography (Table 7) using an internal standard (see footnotes in Tables 1–3). ^1H NMR spectra were recorded on Bruker AC 400 (400 MHz) in $CDCl_3$ with TMS as reference and then compared with authentic samples. The products **2a**, **2b** and **2c** were purified by flash chromatography using methylene chloride and **3a** and **3b** using ethyl acetate/n-pentane (1:5) as eluent.

5.1. Computational details

The reactants **1**, **2**, **3**, **EP** and **DMAD** as well as the corresponding transition states for Diels–Alder reactions were fully optimized without symmetry restrictions (convergence criteria=10^{-4}) with the Hartree–Fock method and using the 6-31G(d) basis set[30] (HF/6-31G(d) calculations). The Gaussian 94 program[31] was used for all calculations. Vibrational frequencies were calculated at the same level of theory to characterize the optimized structures as a minimum or a first-order saddle point on the potential energy surface (the Hessian matrix revealed a single negative eigenvalue for each TS). Previous theoretical studies of cycloaddition have indicated that the activation energies calculated at the Hartree–Fock level are too large, while DFT calculations using the B3LYP hybrid functional[32] have been shown to be in good agreement with experimental activation energy values.[33]

Therefore, the HF/6-31G(d) stationary points were characterized by B3LYP/6-31G(d) single-point calculations (B3LYP/6-31G(d)//HF/6-31G(d) calculations) to obtain more accurate activation energy. The discussion is based on the comparison of experimental results obtained without

Table 7. GC analysis (vector gas is helium (50 kPa) in all cases)

GC column, temperature programme	Compound	rt[a] (min)	Internal standard	rt[a] (min)
OV-1 (12 m×0.22 mm i.d., film thickness 0.1 μm), injector and detector at 250 °C	**1**	4.65	Ethyl diethylmalonate	5.60
80–150 °C[a] with 10 °C min^{-1} then 150–220 °C with 5 °C min^{-1}	**1a**	9.59		
CP-Sil 5CB (25 m×0.32 mm i.d., f. th. 0.12 μm), injector and detector at 280 °C	**2**	5.46	Propyl phthalate	10.36
80–250 °C with 10 °C min^{-1}	**2a**	7.43		
CP-Sil 5CB (idem)	**2**	4.08	Diethyl phthalate	6.50
Injector and detector at 280 °C, 100–250 °C with 10 °C min^{-1}	**2c**	7.29		
OV-1 (12 m×0.22 mm i.d., film thickness 0.1 μm), injector and detector at 280 °C	**3**	2.69	Ethyl benzoate	6.82
50 °C during 2 min then 50–250 °C with 10 °C min^{-1}	**3a**	13.9		

[a] rt, retention time.

solvent at high temperature with computed values on isolated molecule at 0 K. We checked for the reaction **1** that Zero Point Energy (ZPE) corrections reaction do not affect significantly the energy barriers of activation.

References and notes

1. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213–1234.
2. Varma, R. S. *Green Chem.* **1999**, *1*, 43–55.
3. Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851–10870.
4. Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223.
5. Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
6. For a recent and complete review, see. In *Microwaves in organic synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002.
7. Langa, F.; de la Cruz, P.; de la Hoz, A.; Diaz-Ortiz, A.; Diez-Barra, E. *Contemp. Org. Synth.* **1997**, 373–386.
8. Berlan, J.; Giboreau, P.; Lefeuvre, S.; Marchand, C. *Tetrahedron Lett.* **1991**, *32*, 2363–2366.
9. Lewis, D. A.; Summers, J. D.; Ward, T. C.; McGrath, J. E. *J. Polym. Sci. Part A* **1992**, *30*, 1647–1653.
10. Jacob, J.; Chia, L. H. L.; Boey, F. Y. C. *J. Mater. Sci.* **1995**, *30*, 5321–5327.
11. Binner, J. G. P.; Hassine, N. A.; Cross, T. E. *J. Mater. Sci.* **1995**, *30*, 5389–5393.
12. Shibata, C.; Kashima, T.; Ohuchi, K. *Jpn. J. Appl. Phys.* **1996**, *35*, 316–319.
13. (a) Stuerga, D.; Gaillard, P. *Tetrahedron* **1996**, *52*, 5505–5510. (b) Stuerga, D.; Gaillard, P. *J. Microwave Power Electromag. Energy* **1996**, *31*, 87–113.
14. Maoz, R.; Cohen, H.; Sagiv, J. *Langmuir* **1998**, *14*, 5988–5993.
15. Bogdal, D.; Lukasiewicz, M.; Pielichowski, J.; Bednarz, Sz. *Tetrahedron* **2003**, *59*, 649–653.
16. (a) Giguere, R. G.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945–4948. (b) Linders, J. T. M.; Kokje, J. P.; Overhand, M.; Lie, T. S.; Maat, L. *Rec. Trav. Chim. Pays-Bas* **1988**, *107*, 449–454. (c) Lei, B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 4609–4610. (d) Stambouli, A.; Chastrette, M.; Soufiaoui, M. *Tetrahedron Lett.* **1991**, *32*, 1723–1724. (e) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raji, V. S.; Bari, S. S.; Newaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Barakat, K. J. *J. Org. Chem.* **1991**, *56*, 6968–6970. (f) Raner, K. D.; Strauss, C. R.; Vyskoc, F.; Mokbei, L. *J. Org. Chem.* **1993**, *58*, 950–953. (g) Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* **1992**, *57*, 7099–7102. (h) Garrigues, B.; Laporte, C.; Laurent, R.; Laporterie, A.; Dubac, J. *Liebigs Ann.* **1996**, 739–741, see also 743–741. (i) Diaz-Ortiz, A.; Carrillo, J. R.; Diez-Barra, E.; de la Hoz, A.; Gomez-Escalonilla, M. J.; Moreno, A.; Langa, F. *Tetrahedron* **1996**, *52*, 9237–9248. (j) Motorina, I. A.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1997**, *62*, 2098–2105. (k) Diaz-Ortiz, A.; Carrillo, J. R.; Gomez-Escalonilla, M. J.; de la Hoz, A.; Moreno, A.; Prieto, P. *Synlett* **1998**, 1069–1070. (l) Laporte, C.; Oussaid, A.; Garrigues, B. *Compt. Rendus Acad. Sc., Serie IIC* **2000**, *3*, 321–325. (m) de la Hoz, A.; Diaz-Ortiz, A.; Langa, F. In *Microwaves in organic synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; pp 295–343. (n) Essers, M.; Mueck-Lichtenfeld, C.; Haufe, G. *J. Org. Chem.* **2002**, *67*, 4715–4721. (o) Pinto, D. C. G. A.; Silva, A. M. S. *J. Org. Chem.* **2002**, 4715–4721. (p) Leadbeater, N.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145–3148. (q) Almeida, L. M. P. M.; Carrillo, J. R.; Diaz-Ortiz, A.; de la Hoz, A.; Cavaleiro, J. A. S. *Synlett* **2003**, 1415–1418.
17. Commarmot, R.; Didenot, R.; Gardais, J. F. French Patent 84/03496, 1986; *Chem. Abstr.* **1986**, 105, 17442..
18. Hijji, Y. M.; Wanene, J. *Abstr. Pap. Am. Chem. Soc. 2001* **2001**. 221st ORG-497; *Chem. Abstr.* **2001**, 202999.
19. Wynn, C. M.; Klein, P. S. *J. Org. Chem.* **1996**, *31*, 4251–4252.
20. Reed, J. A.; Schilling, C. L., Jr.; Tarvin, R. F.; Rettig, T. A.; Stille, J. K. *J. Org. Chem.* **1969**, *34*, 2188–2191.
21. Effenberger, F.; Ziegler, T. *Chem. Ber.* **1987**, *120*, 1339–1346.
22. Corral, C.; Lissavetzky, J.; Manzanares, I. *Synthesis* **1997**, 29–31.
23. (a) Diaz-Ortiz, A.; Carrillo, J. R.; Cossio, F. P.; Gomez-Escalonilla, M. J.; de la Hoz, A.; Moreno, A.; Prieto, P. *Tetrahedron* **2000**, *56*, 1569–1577. (b) Langa, F.; de la Cruz, P.; de la Hoz, A.; Espildora, E.; Cossio, F. P.; Lecea, B. *J. Org. Chem.* **2000**, *65*, 2499–2507.
24. Buckle, R. N.; Liu, P. Y.; Roberts, E. W. D.; Burnell, D. J. *Tetrahedron* **1999**, *55*, 11455–11464.
25. Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475–488.

26. Loupy, A.; Zaparucha, A. *Tetrahedron Lett.* **1993**, *34*, 473–476.

27. Domingo, L. R.; Picher, M. T.; Zaragoza, J. *J. Org. Chem.* **1998**, *63*, 9183–9189.

28. Kaishnaiah, A.; Narsaiah, B. *J. Fluorine Chem.* **2002**, *113*, 133–137.

29. Tesson, N.; Deshayes, S. *Org. Prep. Proced. Int.* **2000**, *32*, 41–45.

30. (a) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *66*, 217–222. (b) Hehre, W. J.; Radom, L.; Schleyer, V. R. P.; Pople, J. A. *Ab initio molecular orbital theory*; Wiley: New York, 1986.

31. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94, Revision E.1*; Gaussian, Inc.: Pittsburgh, PA, 1995.

32. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

33. (a) Domingo, L. R.; Arno, M.; Andrés, J. *J. Am. Chem. Soc.* **1998**, *120*, 1617–1618. (b) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036–6043. (c) Sbai, A.; Branchadell, V.; Ortuno, R. M.; Oliva, A. *J. Org. Chem.* **1997**, *62*, 3049–3054. (d) Morao, I.; Lecea, B.; Cossio, F. P. *J. Org. Chem.* **1997**, *62*, 7033–7036.