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Preference for β-H elimination in the termination of the Ni-promoted carbonylative cycloaddition of 2-haloethylidene-cycloalkanes and alkynes [1]

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Abstract

The reaction of 2-haloethylidenecycloalkanes (ring size: 5, 6, 7, 8) with either methyl-2-butynoate or 2-butynyl methyl ether and $Ni(CO)_4$ in methanol affords mainly two type of bicyclic compounds: 5-cycloalkenylidenecyclopent-2-enones and 5-(1-cycloalkenyl)cyclopent-2-enones. The origin for the diversion of the process towards elimination instead of alkoxycarbonylation is interpreted as the result of the mutual conformation of the two rings in the intermediates favouring either elimination through enol formation or *syn* β-elimination. In this last case, the terminating step can proceed in two different modes, namely, intraannularly or interannularly. While for the acetylenic ester, the product from interannular elimination is exclusive or predominant regardless of the ring size of the starting halide, for the 2-butynyl methyl ether, the product distribution is found to strongly depend on the nature of the allyl component. Thus, in this case, intraannular elimination is exclusively found in the reaction of the cyclopentylidene halide, while products from interannular elimination are produced in the reaction of the eight-member homologue. Mixtures of the two types of compound are formed from the cyclic 6 and 7 allyl halides. © 1998 Elsevier Science S.A.

Keywords: β-H elimination; 2-haloethylidene-cycloalkanes; acetylenic ester

1. Introduction

Metal mediated inter- or intramolecular cyclisations of different substrates are among the most efficient methods for assembling the different fragments to form the cyclopentane skeleton [1]. In this context, we endeavoured in a systematic rationalisation of the factors involved in the Ni-promoted cyclocarbonylation of allyl halides and alkynes, initially reported by Chiusoli [2–4]. Later, we successfully applied this reaction to different kind of allyl halides [5–8] (Scheme 1**a–c**). A general feature of the process was the absence of β-elimination as the terminating step at the stage of the alkyl–Ni intermediate despite this process, whenever possible, is the general trend in the closely related Pd-catalysed Heck reaction [9–12]. We, initially, attributed this change in behaviour to the higher carbonylating abilities of Ni related to Pd. However, in further findings, we observed that β-elimination could also be prevented in a similar reaction when a σ dative heteroatom was properly placed in the alkyl intermediate [13]. In addition, in a few similar cases, Pd could also carbonylate in preference to β-elimination [14]. Following these observations, we came to the conclusion that the chelation of the keto oxygen might be responsible not only for prevention of β-elimination (in intermediate **D**, by not allowing a *syn*-periplanar mutual arrangement of H and metal) but also for the stabilisation of the alkyl–Ni species for as long as a further carbonyl is coordinated and inserted into the alkyl–Ni bond.

When we applied the present methodology to 2-haloethylidene cycloalkanes to obtain the corresponding 5-cycloalkyl-2-cyclopentenones (Scheme 1**d**), we observed an almost exclusive β-H elimination in the terminating step. The only difference between the prod-

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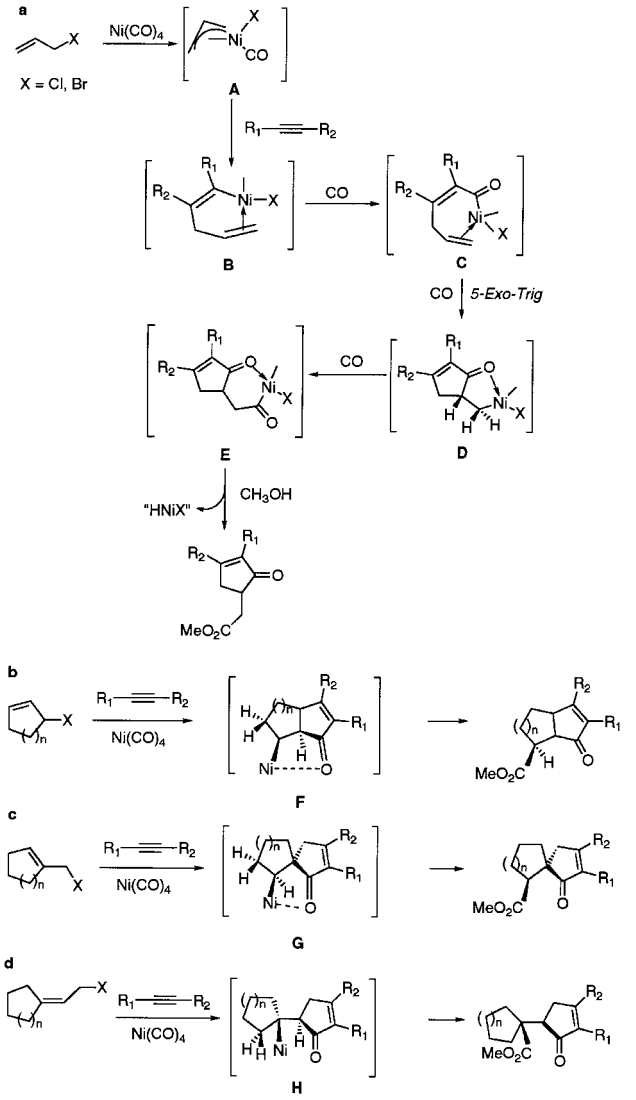
[1] Dedicated to Prof. P.M. Maitlis on occasion of his 65th anniversary.



Scheme 1.

ucts expected in the present case and the ones studied so far was structural (due to the presence of two rings linked by a single bond) [15–20], and therefore, the change in reaction products should be the consequence of conformational interactions between the two rings (their rotation around the common single bond) (e.g., intermediates **D**, **F**, **G** with **H**) [15–20].

Table 1
Reaction of allyl halides **1** and/or **2** with methyl-2-butynoate (**3′**)

Entry	Allyl halide	X	Solvent[a]	Products (yield %)		
1	**1a**+**2a**	Cl	A	**4′a** (91)	–	–
2	**1a**+**2a**	Cl	B	**4′a** (75)	–	–
3	**1b**+**2b**	Cl	A	**4′b** (37)	**6′b** (27)	**8′b** (27)
4	**1b**+**2b**	Cl	B	**4′b** (48)	**6′b** (30)	–
5	**1c**+**2c**	Cl	A	**4′c** (36)	–	–
6	**1c**+**2c**	Cl	B	**4′c** (42)	**6′c** (5)	–
7	**1d**	Br	B	**4′d** (50)	–	–

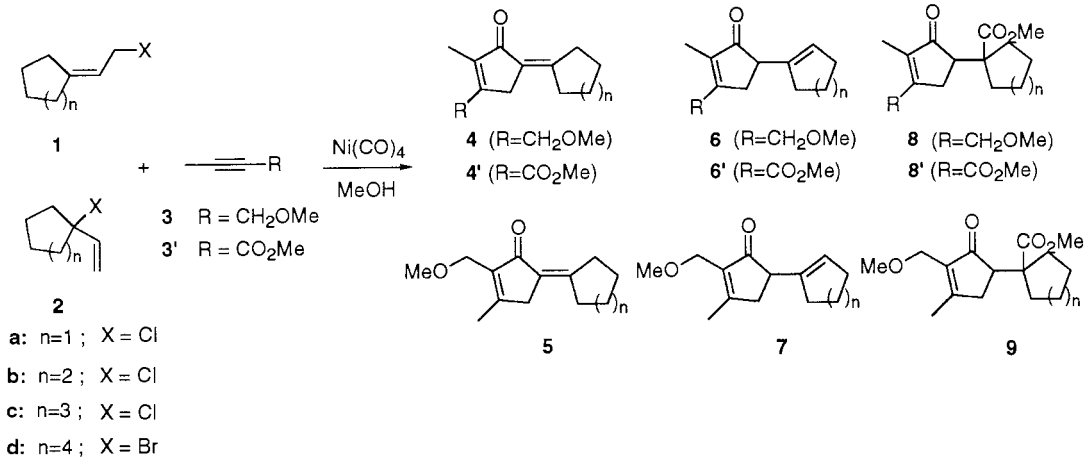
[a]A: MeOH; B: Acetone–MeOH (95:5).

2. Results and discussion

Allyl halides of type **1** and **2** (Scheme 2) were used as single isomers or as mixtures thereof without any difference in the product distribution since the reaction proceeds via a common π-allyl intermediate [5,6] (**A**, Scheme 1).

They were reacted with methyl-2-butynoate or 2-butynyl methyl ether under the presence of $Ni(CO)_4$ in methanol or a 95:5 acetone–methanol mixture.

Three types of products were recorded and characterised from the reaction mixtures. They could be considered arising from a common alkylnickel intermediate (**H**, Scheme 3) followed by methoxycarbonylation at the *ipso* position (**8**) or Ni–H β-elimination in an inter (**4**, **5**) or intraannular (**6**, **7**) way. Product distribution and solvent systems corresponding to the reaction of the different allyl halides with both alkynes are gathered in Tables 1 and 2. In general, yields obtained from methyl-2-butynoate were higher than those from 2-butynyl methyl ether. This feature is generally observed pro-



Scheme 2.

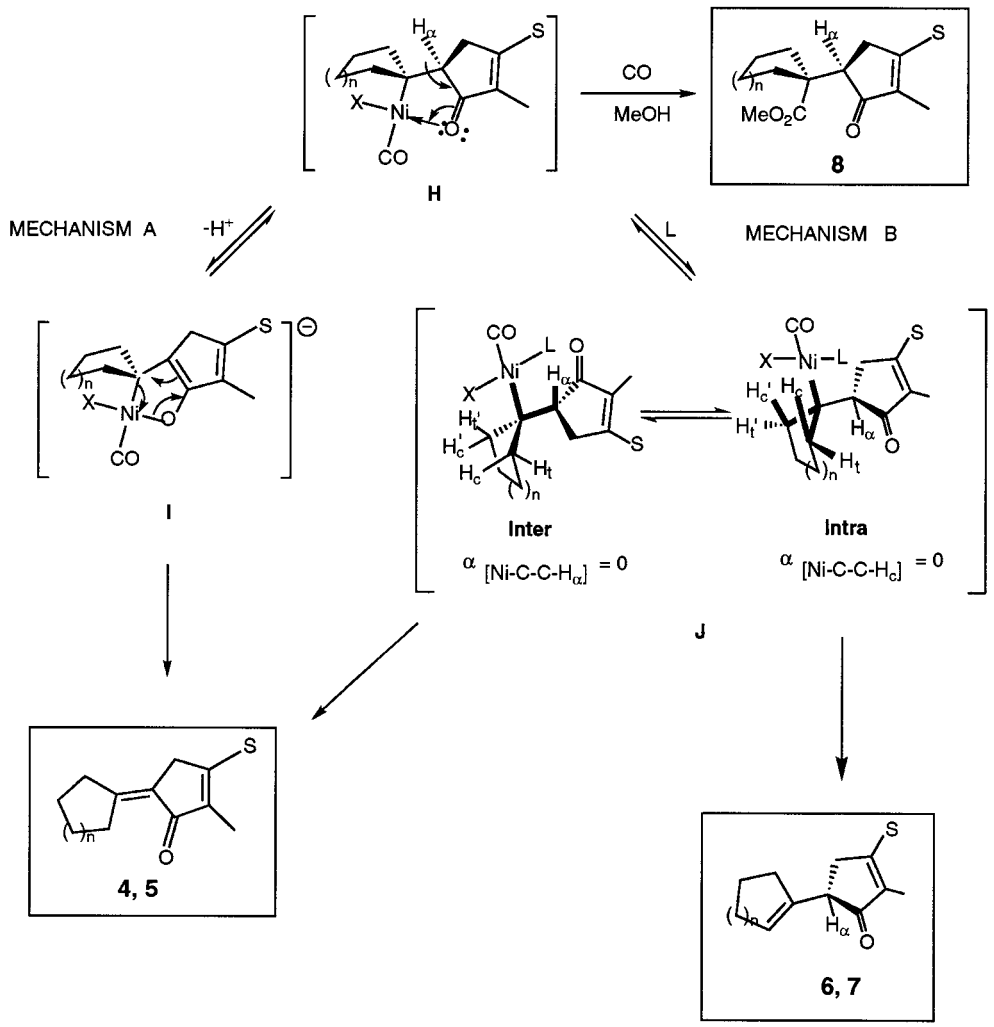
Table 2
Reaction of allyl halides **1** and/or **2** with 2-butynyl methyl ether (**3**) in acetone–methanol (95:5)

Entry	Allyl halides	X	Products (yield %)			
1	**1a** + **2a**	Cl	–	–	**6a** (26)	**7a** (5)
2	**1b** + **2b**	Cl	**4b** (13)	–	**6b** (29)	**7b** (9)
3	**1c** + **2c**	Cl	**4c** (18)	–	**6c** (35)	**7c** (11)
4	**1d**	Br	**4d** (35)	**5d** (9)	–	–

vided that alkyne polyinsertion does not interfere in the termination step [5,6,8].

The replacement of most of methanol as the solvent by acetone proved to be beneficial since it was rising the yields of products of type **4** by preventing the formation of variable amounts of the methoxycarbonyl adduct **8** (Table 1, entries 1–6). A single regioisomer was obtained in all cases with alkyne **3′**. Since yields in cycloadducts are generally lower in reactions involving 2-butynyl methyl ether, **3**, only the acetone–methanol (95:5) solvent system was tried for this alkyne. The results are shown in Table 2. For this alkyne, both regioisomers were observed in all cases for the major reaction product in a ratio roughly approximating to 4:1.

Considering the present results referred to those formerly reported, the most striking observation is the predominance of β-elimination in the terminating step instead of the, so far, more common methoxycarbonylation. This might be attributable to higher restrictions in the achievement of a stabilising five-member chelate ring involving the keto oxygen and the metal. The product distribution obtained from each one of the two alkynes may be interpreted as the result of two competing β-elimination processes (Scheme 3); thus, in mechanism A, enolisation of intermediate **H** to **I** would lead to the formation of an interannular double bond (compounds **4** and **5**); on the other hand, in mechanism B, conformational motion of the two rings around the connecting single bond in intermediate **J** would afford two different coplanar arrangements of the Ni–C–C–H



Scheme 3.

moiety from which two alternative β-elimination processes leading to inter- or intraannular double bond formation may occur [21].

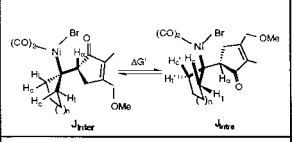
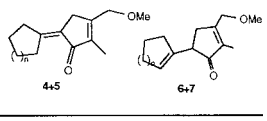
The differences in product distribution arising from the two differently polarised alkynes (**3** and **3′**) suggest a different contribution of each one of the above mechanisms. In reactions involving methyl-2-butynoate (**3′**), interannular elimination products are predominant or exclusive, pointing out that the mechanism A would be strongly favoured. This may be the result of the high acidity inherent to the H_α proton caused by the electron-withdrawing character of $S{=}CO_2CH_3$. [2]

On the contrary, in reactions from 2-butynyl methyl ether (**3**), mechanism B can be anticipated to be preferentially operating. Therefore, products of type **6** and **7** would be expected, in this case, to be mainly obtained. Although interannular elimination can still proceed through β-elimination of the metal with H_α, its coplanar alignment with one of the hydrogens of its ring seems much more probable on statistical grounds. [3] This seems to be the case as reflected in Table 2. However, products from this type of elimination were absent in the reaction of the eight-member halide **1d**, in which case, only products arising from interannular elimination were present in the final mixture.

To gain some insight into the reasons determining the complete change in trend in the elimination step on going from five to eight cyclic member allyl halides (**1a** to **1d**), molecular mechanics calculations [4] were addressed to estimate the relative stability of the different conformers **J** leading to intra- and interannular β-elimination adducts of different ring sizes (Table 3). For each system, two different conformers were analysed with the condition of having a *syn*-periplanar Ni–C–C–H_α arrangement (for $\mathbf{J_{inter}}$) and Ni–C–C–H_c (for $\mathbf{J_{intra}}$), both of them being relative energy minima.

For the allyl halide **1a**, the calculations show that the conformer $\mathbf{J_{intra}}$ should be more stable ($\sim$1.5 kcal mol^{-1}) than the corresponding $\mathbf{J_{inter}}$. The higher stability for that conformer added to the higher statistical probability for an intraannular elimination accounts for the exclusive obtention of intraannularly eliminated products (**6a** + **7a**). The energy gap increases up to 9.5 kcal mol^{-1} (in the opposite sense) for the corresponding intermediates in the eight-member cyclic derivative **1d** pointing out that the difference in the relative conformational energies may lead, in this particular case, to the exclusive formation of products arising from interannular β-elimination (**4d** + **5d**). As from those in between (**1d**, **1c**), mixtures of both type of products are obtained. In these cases, despite $\mathbf{J_{inter}}$ may be more stable than $\mathbf{J_{intra}}$ ($\sim$2–3 kcal mol^{-1}), the higher statistical probability for an intraannular elimination would compensate, by far, the energy gap as deduced from their product distribution. [5] We attribute the increased energy for $\mathbf{J_{intra}}$ related to $\mathbf{J_{inter}}$ on going from the five-ring systems to the eight analogues to the steric interactions between the cyclopentenone methylene and the axial or pseudoaxial substituents of the original ring. The ready β-elimination is in sharp contrast with the preferred alkoxycarbonylation terminating step found in the obtention of fused and spiro bicyclic systems, where at the same stage of the reaction sequence, there is only a single hydrogen available for β-elimination [8], the bicyclic intermediates are far more rigid and the chelated species corresponding to intermediate **H** (**F** and **G**, Scheme 1) are free from severe conformational interactions.

Table 3
Estimated energies of the two opposite conformers $\mathbf{J_{inter}}$ and $\mathbf{J_{intra}}$ by molecular mechanics calculations and ratios of eliminated adducts found in the reaction mixture

	Relative Energies (Kcal/mol)	Found Ratios
		
n	$\Delta H = E_{inter} - E_{intra}$* (Kcal/mol)	Found Ratios (**4+5**) / (**6+7**)
0	1.5	0 : 1
1	-3	1 : 3
2	-2	1 : 2.5
3	- 9.5	1 : 0

[a] It must be born in mind, when reflecting the relative energies into conformer populations, that two different degenerate $\mathbf{J_{intra}}$ intermediates are possible for each one of $\mathbf{J_{inter}}$.

[2] For these products, an alternative Lewis acid catalysed isomerisation of the intraannularly eliminated final products, **6** + **7**, to their thermodynamically more stable interannular counterparts cannot be discarded:
At this respect, **4b** and **4c** might be considered to arise from **6b** and **6c**, respectively, while for the other regioisomer **7**, the corresponding **5b** and **5c** isomers could not be detected.

[3] Both conformers $\mathbf{J_{inter}}$ and $\mathbf{J_{intra}}$ can generate **6** + **7**, and for each one of them, there are two H_c able to eliminate.

[4] Molecular mechanics calculations (MMX) for conformers $\mathbf{J_{inter}}$ and $\mathbf{J_{intra}}$ have been performed by using the program PCMODEL (Molecular Modeling Software for the Macintosh II, Serena Software, 1987, Bloomington). In the first stage, the putative square-planar Ni complex substructure was minimised and further, as a whole, it was incorporated to the bicyclic structure. The conformers of minimum energy for $\mathbf{J_{inter}}$ and $\mathbf{J_{intra}}$ were calculated for each one of the ring size.

[5] It is to be noticed that the acylmetallation step renders an intermediate **H** susceptible of intraannular β-elimination. In addition, β-elimination, as has been stated, is a general and exothermic process (liable to be fast) and even, for rather rigid rings (five-, six-member), after a small conformational motion, $\mathbf{J_{inter}}$ might dispose H_c coplanar with the metal to give products **6** and **7**.

In conclusion, in the $Ni(CO)_4$ mediated carbonylative cycloaddition of alkynes and 2-haloethylidenecycloalkanes, the terminating step consists almost exclusively of a β-hydride elimination affording two kind of products: 5-cycloalkylidene-2-cyclopentenones or 5-(1-cycloalkenyl)-2-cyclopentenones. The diversion from the more common final alkoxycarbonylation step is thought to arise from preferred mutual conformations of the two rings disposing either of the two kinds of hydrogens vicinal to the metal, in the intermediate after ring closure, (on the same ring or on the cyclopentenone ring) coplanar with it and ready for a subsequent β-elimination.

3. Experimental

Caution! $Ni(CO)_4$ is an extremely harmful chemical and special precautions have to be taken in its use. All operations were conducted in a glove box placed in a well-ventilated fume cupboard in a special laboratory.

IR spectra were recorded with a Fourier Bomen–Michelson FT-IR M120 spectrometer and are reported in cm^{-1}. ^1H NMR and ^{13}C NMR were recorded with Gemini 200 Varian and Unity 300 Varian machines. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane, or in ppm relative to the singlet at 7.26 ppm for chloroform-d_1. Coupling constants are reported in Hertz (Hz). ^{13}C NMR are reported in ppm relative to the centre line of a triplet at 77.0 ppm for chloroform-d_1. Routine ^{13}C NMR spectra were fully decoupled by broad-band decoupling. Elemental analyses were performed with a Carlo Erba apparatus (1107 and 1500 Models). TLC was run on F_{254} silica gel plates. Flash chromatography was performed on 230–400 mesh silica gel. $Ni(CO)_4$ was supplied by Strem-Chemicals. Methyl-2-butynoate was furnished by Aldrich and 1-methoxybut-2-yne was prepared in our laboratory by conventional procedures [22,23].

3.1. Synthesis of 2-haloethylidenecycloalkanes

3.1.1. For allyl chlorides **1a–c**

Following the literature procedures, starting from the corresponding cycloalkanones [24,25] after proper reduction [26,27], 2-hydroxyethylidenecycloalkanes were obtained. To a solution of 10 mmol of the allylic alcohol in diethyl ether (15 ml), 1.4 ml (19 mmol) of previously distilled (over linseed oil) thionyl chloride were added. Sixty minutes later, by stirring at room temperature, an additional portion of 0.4 ml of thionyl chloride was added. After one hour, the reaction was quenched with ice-water and the 2-cloroethylidenecycloalkanes were extracted with diethyl ether and washed with brine. Solvent evaporation yielded about 80% of the product that was used without purification. Isomer contents are as follows: For **1a**:**2a** and **1b**:**2b**, approximately 2:1. For **1c**:**2c**, 3:1.

3.1.2. For allyl bromide **1d**

To prepare 2-bromoethylidenecylooctane, 8 mmol of the corresponding allylic alcohol were dropwise added over a solution of 4.8 mmol of phosphorous bromide and 4.8 mmol of pyridine in 10 ml of hexane at $-10°C$. The reaction was worked up as above after stirring for 90 min at room temperature and the product was extracted with hexane. The combined organic layers were washed with brine and dried over $MgSO_4$ and the solvents evaporated in vacuo to give 2-bromoethylidenecyclooctane (75% isolated yield) which was used without further purification.

3.2. General procedure for the synthesis of cyclopentenones

A 50-ml three necked flask provided with magnetic stirring fitted with a thermometer, a gas inlet, and a condenser with its top outlet connected to a mercury valve and a septum was installed in an argon-filled glove box. The outlet of the mercury valve was connected, outside the glove box, to a cold trap containing a solution of iodine in methanol kept at $-20°C$. The trap outlet was directly connected to the exhaust of the fume cupboard. Prior to the reaction, the system was flushed with a stream of Ar and 20 ml of methanol (or a 5% mixture of methanol–acetone) were introduced in the flask with a syringe. A total of 0.3 ml (2.5 mmol) of $Ni(CO)_4$ was added directly from a pressure bottle to a graduated funnel and from this to the reaction flask (temporarily replacing the thermometer fitting). After this addition has been completed and by stirring, a solution of the allyl halide (2.5 mmol) and the corresponding acetylene (1.25 mmol) in 1 ml of the solvent used were added. The reaction mixture was heated to 30–35°C while a cold fluid at $-5°C$ was circulated through the condenser to drive back any volatile $Ni(CO)_4$. The reaction mixture gradually turned from pale yellow to orange-red and finally pale green. Alternatively, the reaction can be also monitored by TLC analysis of aliquots with hexane–ethyl acetate (9:1) as eluent. At the end, the condenser was removed and the outlet of the flask directly connected to the trap containing iodine. Most of the solvent and **any unreacted $Ni(CO)_4$** were evaporated by passing an Ar stream through the reaction flask to the iodine solution (iodine as self-indicator). The dry residue was taken out from the glove box and added 25 ml of a saturated solution of NH_4Cl. After extraction with CH_2Cl_2, the organic phase was washed with brine and dried on magnesium sulfate. Evaporation under vacuum and final flash chromatography with hexane–ethyl acetate (95:5) afforded the products.

3.3. Reaction of 2-chloroethylidenecyclopentane (**1a**) with methyl-2-butynoate (**3′**)

Following the general procedure starting from 325 mg of 2-cloroethylidenecyclopentane as allyl halide and 125 mg of methyl-2-butynoate, in methanol–acetone, 300 mg of crude product was obtained. After flash chromatography, 250 mg of pure cyclopentenone **4′a** were obtained. In a parallel experiment in methanol, 205 mg of the same adduct **4′a** were obtained after purification.

3.3.1. 5-Cyclopentylidene-3-methoxycarbonyl-2-methylcyclopent-2-enone (**4′a**)

IR (CCl_4): 1722, 1695, 1654, 1631, 1222 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.65–1.80 (4H, m, $C(3')H_2$ + $C(4')H_2$); 2.08 (3H, t, $J = 2.4$ Hz, $-CH_3$); 2.43 (2H, t, $J = 6.4$ Hz, $C(2')H_2$); 2.89 (2H, t, $J = 6.4$ Hz, $C(5')H_2$); 3.17 (2H, bs, $C(4)H_2$); 3.82 (3H, s, CH_3OOC-). ^{13}C NMR ($CDCl_3$) δ: 10.3 (q); 25.2 (t); 26.7 (t); 32.6 (t); 32.8 (t); 34.1 (t); 51.9 (q); 125.1 (s); 144.8 (s); 150.8 (s); 161.4 (s); 166.4 (s); 195.9 (s). Anal. Calc. for $C_{13}H_{16}O_3$: C, 70.87%; H, 7.34%. Found: C, 70.43%; H, 7.34%.

3.4. Reaction of 2-chloroethylidenecyclohexane (**1b**) with methyl-2-butynoate (**3′**)

Following the general procedure from 360 mg of starting allyl halide **1b** (+**2b**) and 125 mg of alkyne **3′**, products **4′b** (108 mg; 37%), **6′b** (79 mg; 27%) and **8′b** (98 mg; 27%) were obtained in methanol. In methanol–acetone, only **4′b** (140 mg; 48%) and **6′b** (88 mg; 30%) were obtained.

3.4.1. 5-Cyclohexylidene-3-methoxycarbonyl-2-methylcyclopent-2-enone (**4′b**)

IR (CCl_4): 1724, 1687, 1627, 1436, 1218 cm^{-1}. ^1H NMR ($CDCl_2$) δ: 1.40–1.65 (6H, m, $C(3')H_2$ + $C(4')H_2$ + $C(5')H_2$); 2.08 (3H, t, $J = 2.4$ Hz, $-CH_3$); 2.25 (2H, t, $J = 6$ Hz, $C(2')H_2$); 3.05 (2H, t, $J = 6$ Hz, $C(6')H_2$); 3.24 (2H, q, $J = 2.4$ Hz, $C(4)H_2$); 3.85 (3H, s, $-COOCH_3$). ^{13}C NMR ($CDCl_3$) δ: 10.3 (q); 26.3 (t); 27.5 (t); 28.2 (t); 29.0 (t); 32.2 (t); 34.1 (t); 51.9 (q); 125.2 (s); 144.6 (s); 151.2 (s); 157.9 (s); 166.3 (s); 196.6 (s); MS: 234 (M^+, 100); 203 (18); 175 (44); 154 (61); 131 (26); 105 (37); 91 (46); 81 (86). Anal. Calc. for $C_{14}H_{18}O_3$: C, 71.76%; H, 7.76%. Found: C, 71.60%; H, 7.94%.

3.4.2. 5-(1-Cyclohexenyl)-3-methoxycarbonyl-2-methylcyclopent-2-enone (**6′b**)

IR (CCl_4): 1714, 1690, 1222, 908 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.40–1.60 (6H, m, $C(3')H_2$ + $C(4')H_2$ + $C(5')H_2$); 2.03 (3H, t, $J = 2.4$ Hz, $-CH_3$); 1.90–2.09 (2H, m, $C(6')H_2$); 2.61 (1H, ddq, $J = 18.3$, 2.4, 2.4 Hz, C(4)H); 2.94 (1H, ddq, $J = 18.3$, 7.0, 2.4 Hz, C(4)H); 3.02 (1H, dd, $J = 7.0$, 1.8 Hz, C(5)H); 3.84 (3H, s, $-COOCH_3$); 5.53 (1H, bs, $=C(2')H-$). ^{13}C NMR ($CDCl_3$) δ: 10.0 (q); 22.1 (t); 22.6 (t); 25.2 (t); 25.5 (t); 33.0 (t); 52.1 (d); 53.0 (q); 125.4 (d); 134.4 (s); 147.1 (s); 153.1 (s); 165.9 (s); 210.1 (s).

3.4.3. 5-(1-Methoxycarbonyl)cyclohexyl-3-methoxycarbonyl-2-methylcyclopent-2-enone (**8′b**)

IR (CCl_4): 1728, 1712, 1450, 1434, 1222 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.2–1.9 (10H, m, $C(2')H_2$ + $C(3')H_2$ + $C(4')H_2$ + $C(5')H_2$ + $C(6')H_2$); 1.99 (3H, t, $J = 2.1$ Hz, $-CH_3$); 2.54–2.85 (4H, m, $C(4)H_2$ + C(5)H + C(1′)H); 3.54 (3H, s, $-COOCH_3$); 3.85 (3H, s, $-COOCH_3$). ^{13}C NMR ($CDCl_3$) δ: 9.8 (q); 22.6 (t); 22.7 (t); 25.5 (t); 30.2 (t); 31.0 (t); 31.3 (t); 49.7 (d); 50.2 (d); 51.7 (q); 52.0 (q); 147.6 (s); 151.5 (s); 165.7 (s); 175.5 (s); 208.7 (s). MS: 294 (M^+, 0.4); 263 (4); 234 (9); 168 (4); 154 (100); 141 (19); 122 (12); 94 (22); 81 (30). Anal. Calc. for $C_{16}H_{19}O_5$: C, 65.28%; H, 7.55%. Found: C, 65.25%; H, 7.76%.

3.5. Reaction of 2-chloroethylidenecycloheptane (**1c**) with methyl-2-butynoate (**3′**)

In methanol, from the allyl halide **1c** (+**2c**) (400 mg) and the alkyne **3′** (125 mg), following the above protocol product, **4′c** was obtained (112 mg; 36%). In methanol–acetone (5:95), product **6′c** was also obtained (16 mg; 5%) together with **4′c** (130 mg; 42%).

3.5.1. 5-Cycloheptylidene-3-methoxycarbonyl-2-methylcyclopent-2-enone (**4′c**)

IR (CCl_4): 1724, 1683, 1620, 1220 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.46–1.58 (4H, m, $C(4')H_2$ + $C(5')H_2$); 1.58–1.74 (4H, m, $C(3')H_2$ + $C(6')H_2$); 2.08 (3H, t, $J = 2.4$ Hz, $-CH_3$); 2.42 (2H, t, $J = 6$ Hz, $C(7')H_2$); 3.06 (2H, t, $J = 6$ Hz, $C(2')H_2$); 3.27 (2H, q, $J = 2.4$ Hz, $C(4)H_2$); 3.83 (3H, s, $-COOCH_3$). ^{13}C NMR ($CDCl_3$) δ: 10.3 (q); 26.5 (t); 26.8 (t); 29.4 (t); 29.6 (t); 31.4 (t); 32.4 (t); 35.4 (t); 51.8 (q); 127.7 (s); 144.2 (s); 151.1 (s); 160.5 (s); 166.3 (s); 195.9 (s). MS: 248 (M^+, 100); 220 (30); 154 (27); 126 (110).

3.5.2. 5-(1-Cycloheptenyl)-3-methoxycarbonyl-2-methylcyclopent-2-enone (**6′c**)

IR (film): 1715, 1692, 1630, 1200, 1115 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.15–1.74 (6H, m, $C(4')H_2$ + $C(5')H_2$ + $C(6')H_2$); 1.77–1.88 (2H, m, $C(3')H_2$); 2.02 (3H, t, $J = 2.2$ Hz, $-CH_3$); 2.02–2.20 (2H, m, $C(7')H_2$); 2.54 (1H, ddq, $J = 18.2$, 2.2, 2.2 Hz, C(4)H); 2.92 (1H, ddq, $J = 18.2$, 7.0, 2.2 Hz, C(4)H); 3.04 (1H, dd, $J = 7.0$, 2.2 Hz, C(5)H); 3.80 (3H, s, $-COOCH_3$); 5.70 (1H, t, $J = 6.4$ Hz, C(2′)H). ^{13}C NMR ($CDCl_3$) δ: 10.1 (q); 22.2 (t); 22.5 (t); 24.3 (t); 25.2 (t); 25.6 (t); 33.0 (t); 52.1 (d); 52.8 (q); 124.7 (d); 134.6 (s); 147.0 (s); 153.2 (s); 166.0 (s); 210.1 (s).

3.6. Reaction of 2-bromoethylidenecyclooctane (**1d**) with methyl-2-butynoate (**3′**)

By the general method, starting from **1d** (543 mg) and the acetylene **3′** (125 mg), only **4′d** (164 mg; 50%) was obtained in methanol–acetone.

3.6.1. 5-Cyclooctylidene-3-methoxycarbonyl-2-methylcyclopent-2-enone (**4′d**)

IR (film): 1720, 1679, 1650, 1614, 1218 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.28–1.54 (6H, m, $C(4')H_2$ + $C(5')H_2$ + $C(6')H_2$); 1.69–1.85 (4H, m, $C(3')H_2$ + $C(7')H_2$); 2.07 (3H, t, $J = 2.6$ Hz, $-CH_3$); 2.36 (2H, t, $J = 6$ Hz, $C(2')H_2$); 2.89 (2H, t, $J = 6$ Hz, $C(8')H_2$); 3.21–3.28 (2H, m, $C(4)H_2$); 3.81 (3H, s, $-COOCH_3$). ^{13}C NMR ($CDCl_3$) δ: 10.2 (q); 24.0 (t); 25.7 (t); 26.8 (t); 28.1 (t); 28.2 (t); 30.5 (t); 32.5 (t); 35.3 (t); 51.8 (q); 127.5 (s); 144.0 (s); 151.1 (s); 162.3 (s); 166.3 (s); 195.2 (s). MS: 262 (M^+, 100); 234 (205); 207 (29); 203 (16); 194 (95); 174 (11); 154 (37); 91 (36).

3.7. Reaction of 2-chloroethylidenecyclopentane (**1a**) with 2-butynyl methyl ether (**3**)

In the reaction of allyl halide **1a** (325 mg) and the alkyne **3** (105 mg) in methanol–acetone (5:95), products **6a** (67 mg; 26%) and **7a** (13 mg; 5%) were obtained, separated and independently characterised following the general method.

3.7.1. 5-(1-Cyclopentenyl)-3-methoxymethyl-2-methylcyclopent-2-enone (**6a**)

IR (film): 1703, 1654, 1639, 1330, 1170, 1085 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.72 (3H, bs, $-CH_3$); 1.85 (2H, AB_{syst}, $J_{AB} = 7.2$ Hz, $C(4')H_2$); 2.02–2.18 (1H, m, C(3′)H); 2.20–2.34 (3H, m, C(3′)H + $C(5')H_2$); 2.47 (1H, d, $J = 18.6$ Hz, C(4)H); 2.80 (1H, dd, $J = 18.6$, 7.0 Hz, C(4)H); 3.20 (1H, d, $J = 7.0$ Hz, C(5)H); 3.37 (3H, s, $-OCH_3$); 4.28 (2H, bs, $-CH_2O-$); 5.50 (1H, m, C(2′)H). ^{13}C NMR ($CDCl_3$) δ: 8.2 (q); 23.2 (t); 32.2 (t); 32.7 (t); 33.8 (t); 47.0 (q, $-OCH_3$); 58.9 (d); 70.1 (t, $-CH_2OCH_3$); 126.7 (d); 136.0 (s); 140.9 (s); 166.5 (s); 209.0 (s).

3.7.2. 5-(1-Cyclopentenyl)-2-methoxymethyl-3-methylcyclopent-2-enone (**7a**)

^1H NMR ($CDCl_3$) δ: 1.85 (2H, AB_{syst}, $J_{AB} = 7.8$ Hz, $C(4')H_2$); 2.06–2.16 (1H, m, C(3′)H); 2.15 (3H, s, $-CH_3$); 2.22–2.34 (3H, m, $C(5')H_2$ + C(3′)H); 2.45 (1H, d, $J = 18.6$ Hz, C(4)H); 2.76 (1H, dd, $J = 18.6$, 6.9 Hz, C(4)H); 3.23 (1H, d, $J = 6.9$ Hz, C(5)H); 3.31 (3H, s, CH_3O-); 4.06 (2H, s, $-OCH_2-$); 5.50 (1H, bs, C(2′)H). ^{13}C NMR ($CDCl_3$) δ: 17.4 (q); 23.1 (t); 32.2 (t); 32.7 (t); 38.4 (t); 47.5 (q); 58.5 (d); 63.0 (t); 126.8 (d); 135.9 (s); 140.7 (s); 174.6 (s); 207.5 (s). Anal. Calc. for $C_{13}H_{18}O_2$: C, 75.69%; H, 8.79%. Found: C, 75.44%; H, 8.82%.

3.8. Reaction of 2-chloroethylidenecyclohexane (**1b**) with 2-butynyl methyl ether (**3**)

By the general method, starting from halide **1b** (+**2b**) (360 mg) and the alkyne **3** (105 mg) in methanol–acetone (5:95), products **4b**, **6b** and **7b** were detected in the reaction crude. While **4b** could be isolated by flash chromatography (36 mg; 13%), products **6b** and **7b** came out together (105 mg). By preparative TLC (the same eluent), an almost pure fraction of **7b** was obtained and the product was characterised. The mutual yields were then obtained from relevant signals for both isomers in the ^1H NMR spectrum of the original mixture.

3.8.1. 5-Cyclohexylidene-3-methoxymethyl-2-methylcyclopent-2-enone (**4b**)

IR (film): 1679, 1629, 1448, 1105 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.55–1.68 (6H, m, $C(3')H_2$ + $C(4')H_2$ + $C(5')H_2$); 1.73 (3H, bs, CH_3-); 2.30–2.50 (2H, m, $C(2')H_2$); 3.00–3.20 (4H, m, $C(4)H_2$ + $C(6')H_2$); 3.35 (3H, s, CH_3O-); 4.27 (2H, bs, $-OCH_2-$). ^{13}C NMR ($CDCl_3$) δ: 8.4 (q); 26.4 (t); 28.1 (t); 28.2 (t); 28.5 (t); 32.8 (t); 33.9 (t); 58.8 (t); 69.7 (t); 125.4 (s); 140.4 (s); 153.7 (s); 157.5 (s); 197.4 (s). Anal. Calc. for $C_{14}H_{20}O_2$: C, 76.32%; H, 9.15%. Found: C, 76.35%; H, 9.30%.

3.8.2. 5-(1-Cyclohexenyl)-3-methoxymethyl-2-methylcyclopent-2-enone (**6b**) [6]

^1H NMR ($CDCl_3$) δ: 1.48–1.68 (4H, m, $C(4')H_2$ + $C(5')H_2$); 1.70 (3H, bs, $-CH_3$); 1.70–1.94 (2H, m, $C(3')H_2$); 1.94–2.10 (2H, m, $C(6')H_2$); 2.43 (1H, d, $J = 18.6$ Hz, C(5)H); 2.76 (1H, dd, $J = 18.6$, 7.0 Hz, C(4)H); 2.94 (1H, dd, $J_1 = 7.0$, 2.20 Hz, C(4)H); 3.37 (3H, s, $-OCH_3$); 4.27 (2H, s, $-CH_2O-$); 5.51 (1H, bs, C(2′)H). ^{13}C NMR ($CDCl_3$) δ: 9.5 (q); 23.1 (t); 23.9 (t) 26.4 (t); 26.5 (t); 35.8 (t); 54.9 (q); 60.8 (d); 70.4 (t); 125.0 (d); 135.4 (s); 136.8 (s); 167.2 (s); 210.2 (s).

3.8.3. 5-(1-Cyclohexenyl)-2-methoxymethyl-3-methylcyclopent-2-enone (**7b**)

^1H NMR ($CDCl_3$) δ: 1.50–1.90 (6H, m, $C(3')H_2$ + $C(4')H_2$ + $C(5')H_2$); 1.95–2.12 (2H, m, $C(6')H_2$); 2.17 (3H, bs, $-CH_3$); 2.42 (1H, d, $J = 18$ Hz, C(4)H); 2.75 (1H, dd, $J = 18.0$, 7.0 Hz, C(4)H); 2.99 (1H, dd, $J = 7.1$, 2.2 Hz, C(5)H); 3.32 (3H, s, $-OCH_3$); 4.10 (2H, bs, $-CH_2O-$); 5.53 (1H, bs, C(2′)H). ^{13}C NMR ($CDCl_3$) δ: 17.4 (q); 22.1 (t); 22.6 (t); 25.2 (t); 25.3 (t); 38.5 (t); 53.3 (d); 58.5 (q); 63.1 (t); 124.9 (d); 135.0 (s); 136.6 (s); 175.0 (s); 208.4 (s).

[6] Data obtained from subtraction of the signals of **7b** from those corresponding to the inseparable mixture of **6b** + **7b**.

*3.9. Reaction of 2-chloroethylidenecycloheptane (**1c**) with 2-butynyl methyl ether (**3**)*

Following the general procedure starting from the allyl derivative **1c** (+**2c**) (400 mg) and the acetylene **3** (105 mg) in methanol–acetone (5:95), products **4c** (53 mg; 18%), **6c** (102 mg; 35%) and **7c** (32 mg; 11%) could be separated and independently characterised.

*3.9.1. 5-Cycloheptylidene-3-methoxymethyl-2-methyl-cyclopent-2-enone (**4c**)*

IR (film): 1676, 1623, 1107, 1089 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.40–1.80 (8H, m, C(3′)H_2 + C(4′)H_2 + C(5′)H_2 + C(6′)H_2); 1.78 (3H, bs, –CH_3); 2.39 (2H, t, J = 6.4 Hz, C(2′)H_2); 3.00–3.11 (4H, m, C(4)H_2 + C(7′)H_2); 3.37 (3H, s, –OCH_3); 4.28 (2H, bs, –CH_2O–). ^{13}C NMR ($CDCl_3$) δ: 8.37 (q); 26.7 (t); 27.0 (t); 29.4 (t); 29.7 (t); 30.7 (t); 33.0 (t); 35.2 (t); 58.8 (q); 69.7 (t); 128.0 (s); 140.1 (s); 156.2 (s); 157.0 (s); 196.8 (s). MS: 234 (M^+, 100); 203 (18); 189 (21); 173 (11); 159 (9); 135 (14); 105 (24); 91 (39).

*3.9.2. 5-(1-Cycloheptenyl)-3-methoxymethyl-2-methyl-cyclopent-2-enone (**6c**)*

IR (film): 2921, 2848, 1703, 1650, 1444, 1083 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.20–1.90 (8H, m, C(3′)H_2 + C(4′)H_2 + C(5′)H_2 + C(6′)H_2); 1.72 (3H, bs, –CH_3); 2.00–2.20 (2H, m, C(7′)H_2); 2.38 (1H, d, J = 18.8 Hz, C(4)H); 2.75 (1H, dd, J = 18.8, 6.8 Hz, C(4)H); 2.97 (1H, dd, J = 6.8, 2.6 Hz, C(5)H); 3.38 (3H, s, –OCH_3); 4.28 (2H, bs, –CH_2O–); 5.07 (1H, t, J = 6.4 Hz, C(2′)H). ^{13}C NMR ($CDCl_3$) δ: 8.28 (q); 27.0 (t); 27.1 (t); 28.5 (t); 29.7 (t); 32.7 (t); 33.5 (t); 54.7 (q); 58.9 (d); 70.2 (t); 131.0 (d); 137.0 (s); 141.1 (s); 167.0 (s); 209.4 (s).

*3.9.3. 5-(1-Cycloheptenyl)-2-methoxymethyl-3-methyl-cyclopent-2-enone (**7c**)*

^1H NMR ($CDCl_3$) δ: 1.30–1,78 (6H, m, C(4′)H_2 + C(5′)H_2 + C(6′)H_2); 1.80–192 (2H, td, J = 7.0, 2.8 Hz, C(3′)H_2); 2.01–2.16 (2H, tt, J = 6.4, 3.3 Hz, C(7′)H_2); 2.15 (3H, s, –CH_3); 2.34 (1H, d, J = 18 Hz, C(5)H); 2.70 (1H, dd, J = 18.0, 7.0 Hz, C(4)H); 2.99 (1H, dd, J = 7.0, 2.8 Hz, C(4)H); 3.29 (3H, s, –OCH_3); 4.06 (2H, s, –OCH_2–); 5.69 (1H, t, J = 6.4 Hz, C(2′)H). ^{13}C NMR ($CDCl_3$) δ: 17.4 (q); 26.8 (t); 27.0 (t); 28.4 (t); 29.5 (t); 32.5 (t); 38.1 (t); 55.1 (q); 58.4 (d); 63.0 (t); 130.9 (d); 136.9 (s); 140.8 (s); 175.3 (s); 208.3 (s). MS: 234 (M^+, 100); 202 (106); 187 (30); 173 (25); 159 (15); 131 (27); 105 (24); 91 (55).

*3.10. Reaction of 2-bromoethylidenecyclooctane (**1d**) with 2-butynyl methyl ether (**3**)*

In the reaction of allyl halide **1d** (545 mg) and alkyne **3** (105 mg) in methanol–acetone (5:95), as above, the adducts **4d** (109 mg; 35%) and **5d** (28 mg; 9%) were obtained, separated and characterised.

*3.10.1. 5-Cyclooctylidene-3-methoxymethyl-2-methyl-cyclopent-2-enone (**4d**)*

IR (CCl_4): 1679, 1620, 1446, 1109 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.29–1.84 (13H, m, C(3′)H_2 + C(4′)H_2 + C(5′)H_2 + C(6′)H_2 + C(7′)H_2 + CH_3–C(2)=); 2.34 (2H, t, J = 6.2 Hz, C(8′)H_2); 2.90 (2H, t, J = 6.2 Hz, C(2′)H_2); 3.08 (2H, bs, C(4)H_2); 3.37 (3H, s, –OCH_3); 4.28 (2H, bs, –CH_2O–). ^{13}C NMR ($CDCl_3$) δ: 8.4 (q); 24.1 (t); 25.7 (t); 26.8 (t); 28.1 (t); 28.3 (t); 30.0 (t); 31.2 (t); 35.0 (t); 58.8 (q); 69.7 (t); 127.8 (s); 140.1 (s); 156.8 (s); 157.7 (s); 196.2 (s).

*3.10.2. 5-Cyclooctylidene-2-methoxymethyl-3-methyl-cyclopent-2-enone (**5d**)*

^1H NMR ($CDCl_3$) δ: 1.30–1.82 (10H, m, C(3′)H_2 + C(4′)H_2 + C(5′)H_2 + C(6′)H_2 + C(7′)H_2); 2.14 (3H, s, –CH_3); 2.30 (2H, t, J = 6.0 Hz, C(8′)H_2); 2.88 (2H, t, J = 6.0 Hz, C(2′)H_2); 3.05 (2H, bs, C(4)H_2); 3.34 (3H, s, CH_3O–); 4.10 (2H, s, –OCH_2–). ^{13}C NMR ($CDCl_3$) δ: 16.6 (q); 24.1 (t); 25.7 (t); 26.8 (t); 28.0 (t); 28.2 (t); 29.9 (t); 35.0 (t); 37.7 (t); 58.6 (q); 63.3 (t); 127.8 (s); 139.5 (s); 157.0 (s); 164.6 (s); 189.7 (s).

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