INTRAMOLECULAR ENE REACTIONS *VS* COMPETITIVE PERICYCLIC PROCESSES: THE EFFECT OF SOLVENTS AND SALTS ON THE REACTION OF 5-BROMO-2-(3-METHYL-2-BUTENYLOXY)BENZYLIDENE-MALONIC ACID DIMETHYL ESTER[1,#]

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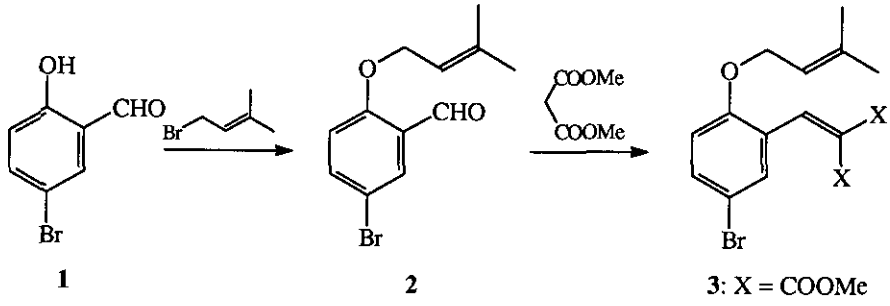
Abstract -The reactivity of 5-bromo-2-(3-methyl-2-butenyloxy)benzylidene-malonic acid dimethyl ester (**3**) was studied in several reaction media. In aprotic solvents intramolecular ene reaction (IER) occurred to give *cis* and *trans* chroman derivatives (**4**) and (**5**), and some kinetic determinations were performed. In protic solvents, besides IER adducts, the products of intramolecular hetero-Diels-Alder reaction and Claisen rearrangement (**10** and **12** respectively) were obtained. In strong protic media, deallylation occurs to give the chromen-2-one derivative (**6**). Finally, the reaction was investigated in acetonic solutions of inorganic perchlorate (barium, lithium, magnesium, and sodium), and these conditions enhanced chemo- and stereo-selectivity and increased the rate. The kinetic effect was dramatic for magnesium perchlorate.

Intramolecular ene reactions (IER) are very useful processes for the formation of carbo-[2] and heterocyclic derivatives,[3,4] and for the syntheses of natural products.[5-8] The cyclization of unactivated 1,6-[9] and 1,7-dienes[10] usually proceeds under severe conditions with poor yields. The introduction of electron withdrawing groups[2] and the use of Lewis acids[11] increases the reactivity, giving rise to systems suitable to be kinetically investigated. Persuing our studies on solvent and salt effects in pericyclic reactions,[1,12] the IER of a 1,7-diene was studied. Due to the previous researches of Tietze and co-workers[2,13] on similar substrates, the suitable system was assumed to be the product of the Knoevenagel condensation of 5-bromo-2-(3-methyl-2-butenyloxy)benzaldehyde (**2**) [obtained by allylation of 5-bromosalicylaldehyde (**1**)] with dimethyl malonate (Scheme 1).

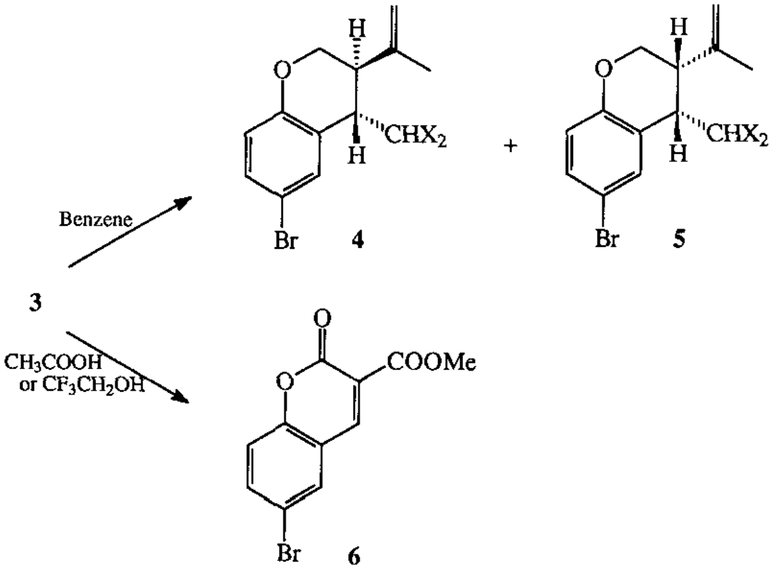
[#] Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

Scheme 1



Before to start the kinetic determinations, the reactivity of **3** was tested in benzene, trifluoroethanol, and acetic acid. Thus **3** was heated in a sealed vial at 130 °C for 60 (benzene) or 6 hours (other solvents). In the first case two cycloadducts were isolated in nearly quantitative yields and by nmr they were shown to be (3R,4R)- and (3S,4R)-6-bromo-4-dicarbomethoxymethyl-3-isopropenylchroman (**4** and **5** respectively, Scheme 2).[14] If the solvent is trifluoroethanol or acetic acid, the main reaction product is 6-bromo-3-methoxycarbonylchromen-2-one (**6**) that was isolated in 66-79% yield.

Scheme 2



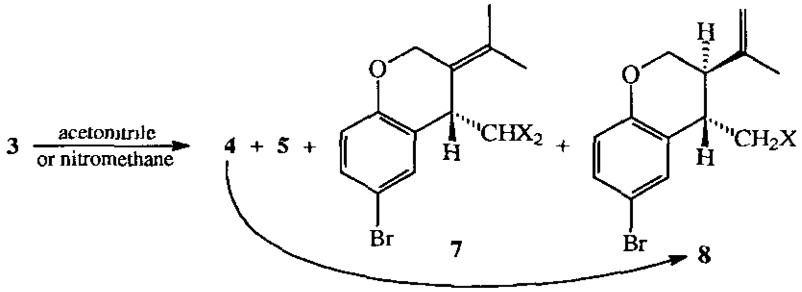
The stereochemistry of **4** and **5** can be determined by nmr. The former has J_{H3H4} = 3.5 Hz, a values consistent with a *trans* diequatorial relation, the equatorial position of H3 being confirmed by the small and equal value of $J_{H2\alpha H3}$ and $J_{H2\beta H3}$ (3.5 Hz). In the case of **5**, H4 is again in an equatorial position (J_{H3H4} = 4 Hz), but H3 is now axial as confirmed by $J_{H2\alpha H3}$ = 11.5 Hz, a value consistent with a *trans*-diaxial relationship.

The formation of **6** was the limit to any accurate kinetic investigation, but the intriguing behaviour of the substrate excited our curiosity to investigate the different reactivity of **3** as a function of the reaction media.

RESULTS

IER of 3 in aprotic solvents. The IER of **3** was performed in five aprotic solvents (polar and apolar)[15] at 130 °C in quartz vials (if the reaction is performed in glass vials, variable amounts of coumarin (**6**) were observed) for the time reported in Table 1. In the case of polar solvents, besides the normal ene adducts (**4**) and (**5**), two other "ene type-products" were obtained in low yields. By nmr and elemental analyses, they were shown to be 6-bromo-4-dicarbomethoxymethyl-3-isopropylidenechroman (**7**) and (3R,4R)-6-bromo-4-carbomethoxymethyl-3-isopropenylchroman (**8**) (Scheme 3).

Scheme 3



Experiments showed that **8** is formed at 130 °C in nitromethane from the ene adduct (**4**). This unusual process was investigated by ^{1}H-nmr following the change in the spectrum of pure **4** in CD_3NO_2 at 130 °C. After 5 hours a complete exchange of the -*CH*(COOMe)$_2$ proton was observed (its relative signal disappeared and the dd system of *H*-4 became a doublet). At the same time a significant amount (19%) of deuterated **8** (**8**-D_2) can be detected in the spectrum. Heating was continued and a regular conversion of **4** into **8**-D_2 was observed. After

Table 1. Product distributions and reaction rates of the IER of **3** at 130 °C in differing aprotic solvents

Solvent	Yield (hours)	**4**	**5**	**7**	**8**	10^5 x k (sec^{-1})[a]
Cyclohexane	82%[b](100)	53	47	0	0	0.82 ± 0.06
Benzene	86%[b] (100)	63	37	0	0	1.08 ± 0.08
Acetone	quant. (80)	64	36	0	0	1.45 ± 0.05
Acetonitrile	quant. (75)	62	28	10	0	2.15 ± 0.15
Nitromethane	quant. (75)	17	28	11	44	(c)

(a)Average of at least three independent kinetic runs; (b)complement to 100 the starting product (**3**). (c)The rate constant was not determined due to the side reactions involved in the overall process.

120 hours, 90% of **8-*D*$_2$** was obtained and, in addition to its signals, if the sealed tube is shaken before recording the spectrum, a singlet is detected at δ 3.35 (a methoxy group, residue of the lost COOMe), whose intensity was comparable to that of **8-*D*$_2$** at δ 3.67. Under the same experimental conditions **5** did a similar process, but with a lower rate (about 2.3 times slower than **4**). This justifies the non-detectable amounts of "**8**-like" product from **5** in the reaction mixture.

The origin of adduct (**7**) cannot be easily explained because it does not derive either from **4** or from **5**. It could be the product of a non-concerted mechanism, but the consistency of a zwitterionic intermediate does not fit the small solvent effect shown by k values in Table 1.

The product distribution, determined by nmr and hplc analysis of the reaction mixtures (see Experimental for details), is reported in Table 1. From these data, only a small increase of the [**4**]/[**5**] ratio with the increase of the solvent polarity is observed.

Even if a small number of solvents can be tested, kinetic determinations were performed by uv-vis spectroscopic analysis of the disappearing **3** at 370 nm in order to obtain informations about what we could call "the solvent effect of the ene reactions".

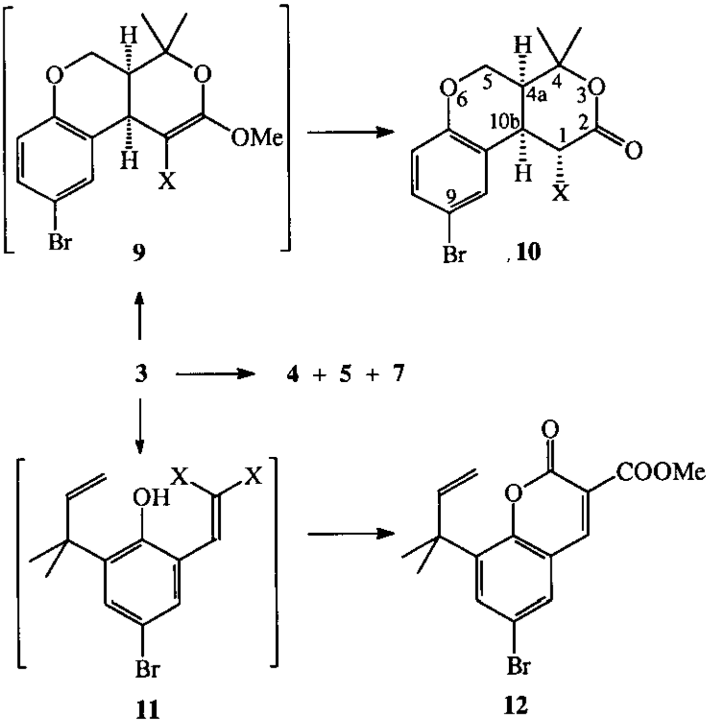
This effect is small, $k_{acetonitrile}/k_{cyclohexane}$ is 2.6, a value in line with the solvent effect of the intermolecular ene-reaction,[1] but the small number of solvents and the impossibility to use protic media (see below) do not allow to clarify the origin of such solvent effect.[16]

Reaction of 3 in protic solvents. The IER reaction of **3** was tested in methanol and *tert*-butanol, ethanol being excluded to avoid the formation of transesterification products. The results, reported in Table 2 and illustrated in Scheme 4, were surprising. Besides the usual ene adducts (**4, 5, 7**), two other products were isolated, and by nmr and elemental analyses they were found to be (1S,4aS,10bS)-9-bromo-1-methoxycarbonyl-4,4-dimethyl-2-oxo-1,2,4,4a,5,10b-hexahydropyran[3,4-*c*]chromene (**10**) and 6-bromo-8-(1,1-dimethyl-2-propenyl)-3-methoxycarbonylchromen-2-one (**12**).

Table 2. Product distributions of the reaction of **3** at 130 °C in *tert*-butanol and methanol.

Solvent	Yield (hours)	**4**	**5**	**7**	**10**	**12**
tert-Butanol	90% (75)	44	40	4	0	12
Methanol	90% (20)	49	23	6	15	7

Scheme 4



The stereochemistry of **10** is determined by taking into account that J_{H1H10b} = 11 Hz is consistent with a *trans*-diaxial relationship, and $J_{H4aH10b}$ = 4.5 Hz is in accordance with a *cis* configuration. H1 exhibits 6% n.O.e. with H5β, and this confirmed the proposed stereochemistry.

The product(**10**)can be assumed to derive from the intramolecular hetero-DA adduct (**9**) that cannot be isolated. **12** is the result of an intramolecular esterification of **11**, this being formed by the Claisen rearrangement of **3**.

The Claisen rearrangement on allyl phenyl ethers is a well-known process extensively investigated by Wolfarth and coworkers.[17] The competition between IER and DA reaction was observed and described by several groups.[2,4,18] Nowadays the above reported IER, DA, and Claisen rearrangement seems to be the first example of three differing competitive intramolecular pericyclic reactions.

Reaction of 3 in strong protic media. When **3** was allowed to react in strong protic media, beside small amounts of the ene adducts (**4, 5,** and **7**), the main reaction product becomes **6**, and in trifluoroacetic acid it is formed in a quantitative yield (Table 3). The formation of **6** can be explained by considering the deallylation of **3** followed by intramolecular transesterification.

Table 3. Product distributions and reaction rates of the reaction of **3** in strong protic media.

Solvent	Yield (hours)	4	5	7	6
Acetic acid[a)]	95% (1.5)	19	9	5	67
Trifluoroethanol[a)]	100% (1)	12	5	4	79
Trifluoroacetic acid[b)]	100% (1)	0	0	0	100

[a)] Reaction performed at 130 °C; [b)] reaction at room temperature.

The effect of perchlorate-acetone solutions. The use of lithium perchlorate in ether has been found very useful for organic synteses.[19,20] The increased reactivity observed in DA cycloaddition[12,21,22] and ER[1] was demostrated to be due to a catalysis promoted by the inorganic cation acting as a Lewis acid.

The effect of barium (BP), lithium (LP), magnesium (MP), and sodium perchlorate (SP) dissolved in acetone on rate and selectivity of the IER of **3** was studied. The rate constants were determined by following the disappearance of the chromophore at 370-380 nm and 30 °C, and the data reported in Table 4 are the average of at least four independent kinetic runs.

Table 4. Rate constants and [**4**]/[**5**] isomer ratio for the IER of **3** at 30 °C in metal perchlorates-acetone solution.

Salt	[M]	[4]/[5]	k (sec^{-1})	k_{rel}
---	---	64:36[a]	1.9×10^{-9} [b]	1
MP	1.00	81:19	$(1.75 \pm 0.07) \times 10^{-3}$	9.1×10^{5}
BP	2.00	84.5:15.5	$(5.40 \pm 0.10) \times 10^{-6}$	2.8×10^{3}
LP	4.00	89:11	$(1.60 \pm 0.10) \times 10^{-5}$	8.4×10^{3}
SP	2.80	---	c	---

a)Value at 130 °C; b)value extrapolated from the Arrhenius diagramm (see Experimental for details); c)no reaction observed at 30 °C.

The reaction performed in perchlorate solutions is faster and more selective than that perfomed in pure solvents and only ene adducts (**4**) and (**5**) were observed by nmr and hplc analysis of the reaction mixture.The [**4**]/[**5**] ratio is not significantly influenced by the inorganic salts, but the important result derived from data reported in Table 4, is that the IER of **3** is strongly accelerated by the presence of inorganic perchlorates. Taken as a reference the extrapolated rate constant at 30 °C in pure acetone, the relative rate is increased up to 2,800 and 8,300 times in BP- and LP-acetone solutions (2.0 and 4.0 M respectively). SP has no evident catalytic effect, while MP gives a very strong acceleration: the rate increases 9.1×10^{5} times in a 1.0 M solution.

CONCLUSION

Unfortunately, the starting target, to investigate the solvent effect on IER of **3**, was impossible to reach because the change of the solvent gave rise to differing competitive reactions.

Fortunately, chemoselectivity was enough various and solvent-dependent to become itself the target of the research.

Aprotic solvents gave IERs only and a small solvent effect was observed, this being compatible either with specific or non specific solute-solvent interactions.

Protic solvents, besides IERs, gave intramolecular HDA reaction and a Claisen rearrangement. Whereas the latter can be justified as the result of the polar character specific of these solvents also,[17,23] the development of the HDA adduct (**10**) cannot be at moment rationalized.

The effect of perchlorate-acetone solutions is important. These reaction media can be used to lower the experimental conditions, to increase the *trans* stereoselectivity, and to support a specific solute-solvent interaction as the origin of the solvent effect observed in Table 1. The dramatic rate acceleration in perchlorate solutions is the clear result of a Lewis acid catalysis and it is inconsistent with a change of polarity of the media.[23] A significant divergency is observed between the effects of MP and BP or LP solutions. The former gives rise to rate accelerations of the same order of those observed for the catalysis of the intramolecular HDA reactions with CF_3COOH.[24] The latter cations have at least 100 times lower catalytic effect than magnesium and this, perhaps, opens new horizons in the field of molecular recognition between substrate and Lewis acid when this is Mg^{2+}.[25] The peculiar effect of the magnesium ion is supported by the activation parameters reported in Table 5. The activation entropy in MP 1.0 M is still compatible with a concerted process,[1,12] but is about 7 e.u. lower than those in BP 2.0 M and LP 4.0 M, these latter values being very close to the activation entropy in pure acetone.

Table 5. Rates and activation parameters of the IER of **3** in the presence of differing perchlorates and in pure acetone.

T/°C	k (sec^{-1}) acetone	MP 1.0 M	BP 2.0 M	LP 4.0 M
15	---	$(5.23 \pm 0.03) \times 10^{-4}$	---	---
20	---	$(8.75 \pm 0.05) \times 10^{-4}$	$(2.1 \pm 0.1) \times 10^{-6}$	$(6.6 \pm 0.1) \times 10^{-6}$
25	---	$(1.30 \pm 0.05) \times 10^{-3}$	$(3.5 \pm 0.1) \times 10^{-6}$	$(1.2 \pm 0.1) \times 10^{-5}$
30	---	$(1.75 \pm 0.07) \times 10^{-3}$	$(5.4 \pm 0.1) \times 10^{-6}$	$(1.6 \pm 0.1) \times 10^{-5}$
35	---	---	$(7.7 \pm 0.1) \times 10^{-6}$	$(2.5 \pm 0.1) \times 10^{-5}$
110	$(4.85 \pm 0.1) \times 10^{-6}$	---	---	---
120	$(7.0 \pm 0.1) \times 10^{-6}$	---	---	---
130	$(1.45 \pm 0.05) \times 10^{-5}$	---	---	---
140	$(2.7 \pm 0.1) \times 10^{-5}$	---	---	---
$\Delta H^{\ddagger(a)}$	17.7 ± 0.5	13.4 ± 0.7	15.0 ± 1	15.0 ± 1
$-\Delta S^{\ddagger(b)}$	37.0 ± 2	27.0 ± 2	34.0 ± 3	32.0 ± 3

[a] Kcal mol^{-1}; [b] cal K^{-1} mol^{-1}.

EXPERIMENTAL

Melting points were determined by the capillary method. Elemental analyses were obtained with a C. Erba mod. 1106 CHN analyzer. ^{1}H- and ^{13}C-Nmr spectra were recorded on a Bruker 300 spectrometer, ir spectra (nujol mulls) on a Perkin Elmer 983 spectrophotometer. The stationary phase for the column chromatography was Merck silica gel (230-400 mesh ASTM).

Materials. 5-Bromosalicylaldehyde (**1**) was a commercial product. The solvents for the kinetic runs were distilled anhydrous UV-Vis spectroscopic grade reagents. The metal perchlorates were grade reagent; with the exclusion of MP, all other salts were dried under vacuum at 140 °C for 8 hours (caution: all perchlorates are potential explosives and must be handled with care).[26]

5-Bromo-2-(3-methyl-2-butenyloxy)benzaldehyde (2). 4.02 g of **1** (20 mmol) were dissolved in 20 ml of DMF and added, at 0° C, to a suspension of 0.62 g of NaH (25.8 mmol) in 10 ml of DMF. Dimethylallyl bromide (3.28 g, 22 mmol) was then added to the solution, and the stirring was continued for 5 h at 0 °C. The reaction mixture was then quenched in ice and extracted with dichloromethane (3 x 20 ml). The organic layers were washed with water, dried over Na_2SO_4, and evaporated to dryness to give 5.11 g (95% yield) of **2** as pale yellow oil that can be purified by vacuum distillation (bp = 122-125 °C at 0.05 mbar). Ir: 1690 cm^{-1}. ^{1}H-Nmr ($CDCl_3$), δ: 10.38 (s, 1H, -C*H*O), 7.89 (d, *J* = 3 Hz, 1H, *H*-6), 7.57 (dd, *J* = 3 and 9 Hz, 1H, *H*-4), 6.87 (d, *J* = 9 Hz, 1H, *H*-3), 5.46 (t, *J* = 7.5 Hz, 1H, -C*H*=CMe$_2$), 4.62 (d, *J* = 7.5 Hz, 2H, -OC*H*$_2$), 1.82 and 1.77 [s + s, 3H + 3H, -CH=C(C*H*$_3$)$_2$]. Anal. Calcd for $C_{12}H_{13}O_2Br$: C, 53.55; H, 4.9. Found: C, 53.4; H, 5.0.

5-Bromo-2-(3-methyl-2-butenyloxy)benzylidenemalonic acid dimethyl ester (3). A solution of **2** (0.540 g, 2 mmol) and dimethyl malonate (0.264 g, 2 mmol) in 3 ml of methanol with a drop of piperidine and acetic acid was stirred at room temperature for 36 h. The solution was evaporated to dryness and the residue was column chromatographed (eluant: cyclohexane - ethyl acetate = 85 - 15). The second fraction gives 0.52 g of **3** (64% yield), crystallized from ethanol to give white crystals, mp 54-55 °C. Ir: 1728, 1634, and 1622 cm^{-1}. ^{1}H-Nmr ($CDCl_3$), δ: 8.02 [s, 1H, -C*H*=C(COOR)$_2$], 7.44 and 7.42 (m, 2H, *H*-4 and *H*-6), 6.78 (d, *J* = 9 Hz, 1H, *H*-3), 5.44 (t, *J* = 7.5 Hz, 1H, -C*H*=CMe$_2$), 4.55 (d, *J* = 7.5 Hz, 2H, -OC*H*$_2$-), 3.85 and 3.82 (s + s, 3H + 3H, -OC*H*$_3$), 1.78 and 1.72 [s + s, 3H + 3H, -CH=C(C*H*$_3$)$_2$]. Anal. Calcd for $C_{17}H_{19}O_5Br$: C, 53.3; H, 5.0. Found: C, 53.0; H, 4.9.

IER of 3. 0.3 g of **3**, dissolved in 3 ml of toluene, were heated at 130 °C in a sealed vial. After 5 days the reaction was completed; the solution was evaporated and the residue was column chromatographed (eluant: cyclohexane - ethyl acetate = 95 - 5) The first fraction gave (3S,4R)-6-bromo-4-dicarbomethoxymethyl-3-isopropenylchroman (**5**) as white crystals (0.14 g, 47% yield), mp 80-81 °C (from petrol ether). Ir: 1732 and 1640 cm^{-1}. ^{1}H-Nmr (CD_3COCD_3), δ: 7.43 (dd, J = 9 and 3 Hz,. 1H, *H*-7), 7.18 (d, J = 3 Hz, 1H, *H*-5), 6.72 (d, J = 9 Hz, 1H, *H*-8), 4.96 and 4.68 (bs + bs, 1H + 1H, *vinylic protons*), 4.35 (t, $J_{H2\alpha H2\beta} = J_{H2\alpha H3}$ = 11.5 Hz, 1H, *H*-2α), 4.27 (ddd, $J_{H2\beta H3}$ = 4 Hz, $J_{H2\beta H4}$ = 2 Hz, $J_{H2\alpha H2\beta}$ = 11.5 Hz, 1H, *H*-2β), 3.99 (m, 1H, *H*-4), 3.69 and 3.33 (s + s, 3H + 3H, -O*CH_3*), 3.59 [d, J = 6.5 Hz, 1H, -C*H*$(COOMe)_2$], 2.61 (m, J_{H3H4} = 4 Hz, 1H, *H*-3), and 1.82 (s, 3H, *allylic methyl*). Anal. Calcd for $C_{17}H_{19}O_5Br$: C, 53.3; H, 5.0. Found: C, 53.4; H, 5.0. The second fraction gave (3R,4R)-6-bromo-4-dicarbomethoxymethyl-3-isopropenylchroman (**4**) as white crystals (0.14 g, 47% yield), mp 73-74 °C (from petrol ether/diisopropyl ether). Ir: 1747, 1732 and 1641 cm^{-1}. ^{1}H-Nmr (CD_3COCD_3), δ: 7.25 (m, 2H, *H*-5 and *H*-7), 6.71 (d, J = 9 Hz, 1H, *H*-8), 4.85 and 4.81 (bs + bs, 1H + 1H, *vinylic protons*), 4.30 (dd, $J_{H2\alpha H2\beta}$ = 12 Hz, $J_{H2\alpha H3}$ = 3.5 Hz, 1H, *H*-2α), 4.24 (ddd, $J_{H2\beta H3}$ = 3.5 Hz, $J_{H2\beta H4}$ = 1.5 Hz, $J_{H2\alpha H2\beta}$ = 12 Hz, 1H, *H*-2β), 3.86 [d, J = 8 Hz, 1H, -C*H*$(COOMe)_2$], 3.72 and 3.57 (s + s, 3H + 3H, O*CH_3*), 3.70 (m, 1H, *H*-4), 2.65 (q, J = 3.5 Hz, 1H, *H*-3), and 1.82 (s, 3H, *allylic methyl*). Anal. Calcd for $C_{17}H_{19}O_5Br$: C, 53.3; H, 5.0. Found: C, 52.9; H, 5.0.

The chromatographic separation of the reaction run in nitromethane gives three fractions. The first one corresponds to (3R,4R)-6-bromo-4-carbomethoxymethyl-3-isopropenylchroman (**8**) as colourless oil. Ir: 1733 and 1642 cm^{-1}. ^{1}H-Nmr ($CDCl_3$), δ: 7.24 (d, J = 2 Hz, 1H, *H*-5), 7.20 (dd, J = 8 and 2 Hz, 1H, *H*-7), 6.69 (d, J = 8 Hz, 1H, *H*-8), 4.93 (m, 1H, *vinylic proton*), 4.83 (s, 1H, *vinylic proton*), 4.16 (dd, $J_{H2\alpha H2\beta}$ = 11 and $J_{H2\beta H3}$ = 3.5 Hz, 1H, *H*-2β), 4.07 (dd, $J_{H2\alpha H3}$ = 6.5 Hz, $J_{H2\alpha H2\beta}$ = 11 Hz, 1H, *H*-2α), 3.71 (s, 3H, -O*CH_3*), 3.40 (q, J = 6.5 Hz, 1H, *H*-4), 2.76 (d, J = 6.5 Hz, 2H, C*H_2*COOMe), 2.46 (dt, $J_{H2\beta H3}$ = 3.5 Hz, $J_{H2\alpha H3} = J_{H3H4}$ = 6.5 Hz, 1H, *H*-3), and 1.78 (s, 3H, *allylic methyl*). Anal. Calcd for $C_{15}H_{17}O_3Br$: C, 55.4; H, 5.3. Found: C, 55.3; H, 5.4. The second fraction gives **5**, while the third one gives a mixtures of **4** and 6-bromo-4-dicarbomethoxymethyl-3-isopropylidenechroman (**7**). **4** was separated out by crystallization with petrol ether and the mother liquors were found to be an unseparable mixture of **4** and **7** in the ratio 1:2. From the ^{1}H-nmr of the mixture, the following signals can be assigned to **7**, δ: 7.2-6.7 (m, 3H, *aromatic protons*), 4.87 (d, $J_{H2\alpha H2\beta}$ = 13 Hz, 1H, *H*-2), 4.67 (m, 1H, *H*-2), 4.53 [dd, J = 10 and 1.5 Hz, 1H, *H*-4), 3.80 (d, 1H, J = 10 Hz, C*H_2*$(COOMe)_2$], 3.68 and 3.66 (s + s, 3H + 3H, -OC*H*$_3$), 1.82 and 1.70 (d + d, *J* = 1.5 Hz, 3H + 3H, *allylic methyls*). ^{13}C-Nmr ($CDCl_3$), δ: 167.9, 167.5, 153.6, 134.2, 131.6, 131.4, 127.1, 122.4, 118.7, 112.5, 65.45, 57.0, 52.5, 52.4, 38.8, 20.7, and 20.3. ^{1}H-Nmr (CD_3NO_2) of **8**-*D*$_2$, δ: 7.34 (d, *J* = 3 Hz, 1H, *H*-5), 7.22 (dd, *J* = 3 and 9 Hz, 1H, *H*-7), 6.72 (d, *J* = 9 Hz, 1H, *H*-8), 4.94 (bs, 1H, *vinylic proton*), 4.83 (s, 1H, *vinylic proton*), 4.30-4.18 (m, 2H, *H*-2), 3.71 (s, 3H, -OC*H*$_3$), 3.41 (d, *J* = 6.5 Hz, 1H, *H*-4), 2.53 (m, 1H, *H*-3), and 1.81 (s, 3H, *allylic methyl*).

Reaction of 3 in methanol. 1.0 g of **3** (2.6 mmol) was dissolved in 3 ml of methanol and heated in a sealed quartz vial at 130 °C for 20 h. The reaction mixtures was column chromatographed as previously described and four fractions were collected. The first one corresponds to **5** (0.21 g, 21%), while the second fraction is a mixture of **4** and **7**: 0.44 g of **4** (44%), and 0.05 g of **7** (5%). The third fraction gives 0.06 g (6%) of 6-bromo-8-(1,1-dimethyl-2-propenyl)-3-methoxycarbonylchromen-2-one (**12**) as white crystals, mp = 137-138 °C (from ethanol). Ir: 1763, 1700 and 1617 cm^{-1}. ^{1}H-Nmr ($CDCl_3$), δ: 8.42 (s, 1H, *H*-4), 7.70 and 7.60 (d + d, *J* = 3 Hz, 1H + 1H, *H*-5 and *H*-7), 6.20 (dd, *J* = 10.5 and 17 Hz, 1H, *vinylic proton*), 5.12 (dd, *J* = 10.5 and 1 Hz, 1H, *vinylic proton*), 5.07 (dd, *J* = 17 and 1 Hz, 1H, *vinylic proton*), 3.96 (s, 3H, -OC*H*$_3$), and 1.60 (s, 6H, *methyls*). Anal. Calcd for $C_{16}H_{15}O_4Br$: C, 54.7; H, 4.3. Found: C, 54.7; H, 4.25. The last fraction gives 0.13 g (13%) of (1*S*,4a*S*,10b*S*)-9-bromo-1-methoxycarbonyl-4,4-dimethyl-2-oxo-1,2,4,4a,5,10b-hexahydropyran[3,4-*c*]chromene (**10**) as white crystals, mp 151-153 °C (from petrol ether). Ir: 1735, and 1708 cm^{-1}. ^{1}H-Nmr ($CDCl_3$), δ: 7.30 (dd, *J* = 8 and 2 Hz, 1H, *H*-8), 7.09 (d, *J* = 2 Hz, 1H, *H*-10), 6.76 (d, *J* = 8 Hz, 1H, *H*-7), 4.51 (m, $J_{H4aH5\alpha}$ = 4.5, $J_{H5\alpha H5\beta}$ = 12, $J_{H5\alpha H10b}$ = 1.5 Hz, 1H, *H*-5α), 4.03 (t, $J_{H5\alpha H5\beta}$ = $J_{H5\beta H4a}$ = 12 Hz, 1H, *H*-5β), 3.95 (m, J_{H1H10b} = 11, $J_{H4aH10b}$ = 4.5 Hz, 1H, *H*-10b), 3.89 (s, 3H, -OC*H*$_3$), 3.58 (d, *J* = 11 Hz, 1H, *H*-1), 2.32 (dt, $J_{H4aH5\alpha}$ = $J_{H4aH10b}$ = 4.5, $J_{H5\beta H4a}$ = 12 Hz, 1H, *H*-4a), 1.66 and 1.49 (2s, 3H + 3H, *methyls*). ^{13}C-Nmr ($CDCl_3$), δ: 169.2, 165.3, 151.8, 132.0, 131.0, 124.2, 118.85, 112.75, 82.4, 62.4, 53.2, 51.7, 37.05, 32.6, 29.1, and 25.8. Anal. Calcd for $C_{16}H_{17}O_5Br$: C, 52.05; H, 4.6. Found: C, 52.3; H, 4.5. $M^{+\cdot}$ = 368.

Reaction of 3 in trifluoroacetic acid. 0.1 g of **3**, dissolved in 2 ml of trifluoroacetic acid, were stirred at room temperature for 1 h. The mixture was quenched in saturated $NaHCO_3$ solution and extracted with dichloromethane (2 x 20 ml). The organic phase was dried and evaporated to give 70 mg (95% yield) of **6** as white crystals, mp 172-173 °C (from methanol). Ir: 1750, 1696 and 1616 cm^{-1}. ^{1}H-Nmr ($CDCl_3$), δ: 8.47 (s, 1H, *H*-4), 7.75 (d, *J* = 2 Hz, 1H, *H*-5), 7.73 (dd, *J* = 2 and 8 Hz, 1H, *H*-7), 7.25 (d, *J* = 8 Hz, 1H, *H*-8), and 3.98 (s, 3H, -OC*H*$_3$). Anal. Calcd for $C_{11}H_7O_4Br$: C, 46.7; H, 2.5. Found: C, 46.5; H, 2.4.

Determination of the product distribution. This was performed by ^{1}H-Nmr: 15-20 mg of **3** were allowed to react in the pure solvent (3 ml - 130 °C) or in the perchlorates solutions (5 ml - 30 °C). In the first case the solvent was evaporated to dryness and the residue dissolved in $CDCl_3$, while the reaction mixtures in the perchlorate solutions[27] were quenched in water, extracted with dichloromethane, evaporated to dryness, the residue dissolved in $CDCl_3$. and the ^{1}H-Nmr was then recorded. The data reported in Tables 1 and 2 are the average of at least three independent experiments, and the error is in the limit ± 0.5 %. These data were confirmed by hplc analysis of the reaction mixtures.

The hplc determinations were performed on a Waters Associated ALC/CPC 244 liquid chromatograph, with a detector operating at 231 nm, on a stainless steel column (25 cm x 4 mm internal diameter) pre-packed with Lichrosphere Si 100 (5 μm) Altech; eluant: cyclohexane-ethyl acetate 90:10; flow 0.6 ml/min; retention times: **8**, 9.36; **5**, 10.8; **3**, 12.4; **7**, 14.0; **4**, 14.8; **12**, 23.5; **10**, 39.7; **6**, 44.0 min.

Kinetic determinations. The overall reaction rates were measured by following the disappearance of the chromophore **3** on a Perkin Elmer Lambda 16 spectrophotometer provided with a thermostatted cell transport assembly and an automatic multicell programmer. The solutions were measured in 1.00 cm OS Hellma couvettes with 3 ml capacity; measuraments were taken at wavelengths in the range 370-380 nm.

The rate constants for the ene reaction of **3** in pure solvents were determined as follow. About 20 mg of **3** were placed in a 25 ml volumetric flask, that was then filled with the required solvent. Seven samples in quartz vials were prepared for each run. At t=0, the samples were placed in a thermostat at the required temperature, and the initial absorbance of the solution was determined on a further sample. At appropriate time intervals (5-100 min, depending on solvent and temperature), the reaction was quenched and the residual absorbance of **3** was determined.

For the determination of the rate constants in perchlorate-acetone solutions, the procedure was as follow. The needed amount of metal perchlorate was weighed in a 10 ml volumetric flask that was filled with acetone; variable amounts of the salt solutions (2.0-2.5 ml) were directly thermostatted at the required temperature. Amounts of **3** were then added to the solution in order to obtain absorbance values in the range 0.8-1.6 A. After vigorous mixing the kinetic determinations were initiated.

ACKNOWLEDGEMENTS

The financial support of the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the Consiglio Nazionale delle Ricerche (CNR) is warmly acknowledged.

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Received 6th June, 1994