Experimental evidence for a [2 + 2] mechanism in the Lewis acid-promoted formation of α,β-unsaturated esters from ethoxyacetylene and aldehydes. Synthesis and characterisation of 4-ethoxyoxetes.

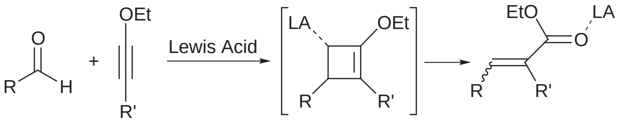
Magali Oblin,[a] Jean-Luc Parrain,[b] Michel Rajzmann[b] and Jean-Marc Pons*[a]†

[a] *Laboratoire Réactivité en Synthèse Organique (RéSo), UMR 6516, Faculté de St-Jérôme, boîte D12,13397 Marseille Cedex 20, France*

[b] *Laboratoire de Synthèse Organique, ESA 6009, Faculté de St-Jérôme, boîte D12, F-13397 Marseille Cedex 20, France*

4-Ethoxy-2*H*-oxetes 3a–c were prepared from ethoxyacetylene and alkoxy aldehydes 1a–c through $MgBr_2$–Et_2O promoted [2 + 2] cycloaddition reaction and were characterized at room temperature; their synthesis, which could occur *via* the formation of a chelate, establishes cycloaddition as the initial step in the formation of α,β-unsaturated esters 4a–c.

The formation of α,β-unsaturated esters from aldehydes or ketones and alkoxyacetylenes, under Lewis acid catalysis was first reported by Vieregge *et al.* in 1959.[1] The reaction immediately met with success as demonstrated in a review article published seven years later by the same authors.[2] In the same paper, the authors proposed that the mechanism involves the formation of an intermediate alkoxyoxete and its conrotatory ring-opening to give the corresponding α,β-unsaturated ester (Scheme 1).



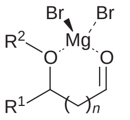
Scheme 1

The strongest evidence supporting such a mechanism at that time was the isolation by Middleton of an alkoxyoxete resulting from the non-catalyzed reaction between hexafluoroacetone and ethoxyacetylene.[3] Furthermore this oxete underwent a rearrangement to yield the corresponding unsaturated ester. Since then this reaction has attracted many experimental studies[4] and has even found application in synthesis where it can sometimes be used instead of the Wittig reaction.[5] However, to the best of our knowledge, no experimental evidence of the occurrence of a non-metallated oxete[6] in a Lewis acid catalyzed process has yet been reported. This is probably due to the instability of oxetes which have been seldom isolated or characterized.[7] Examples of alkoxyoxetes are also very scarce: in addition to the examples reported by Middleton[3] and Zaitseva *et al.*,[6] two others can be found in the literature.[8,9]

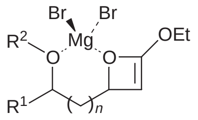
As part of an ongoing interest in Lewis acid-promoted [2 + 2] cycloadditions involving aldehydes,[10] we report the observation and characterization, at room temperature, of 2-ethoxy-2*H*-oxetes **3a**–**c**.

3-Benzyloxytetradecanal **1a** reacts with ethoxyacetylene **2** under $MgBr_2$–Et_2O catalysis in CH_2Cl_2 to yield after 30 min 2-(2-benzyloxytridecyl)-4-ethoxy-2*H*-oxete **3a** as a 4 : 1 mixture of diastereomers (Scheme 2, Table 1, entry 1).‡ 4-Ethoxy-2*H*-oxetes **3b,c**§ were also obtained (both as 9 : 1 mixtures of diastereomers) from aldehydes **1b,c** and were observed under the same conditions (Scheme 2, Table 1, entries 3 and 4).

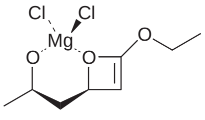
The obtention of oxetes **3a**–**c** could result from the formation of chelate **A**[11] which then would lead to the 'bicyclic' cycloadduct-chelate **B**. The rigidity of the chelate structure of **B**, *i.e.* its 'bicyclic' structure, under the reaction conditions, could then prevent the ring opening rearrangement. We have undertaken *ab initio* calculations on a model chelate **C** to establish that such an intermediate is indeed a minimum on a potential energy surface. Calculations were run at the HF/6-31G* level of theory. The total energy of **C** was found to be −1693.424205 au.



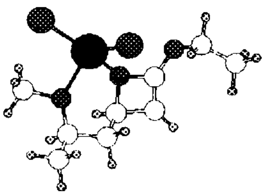
A



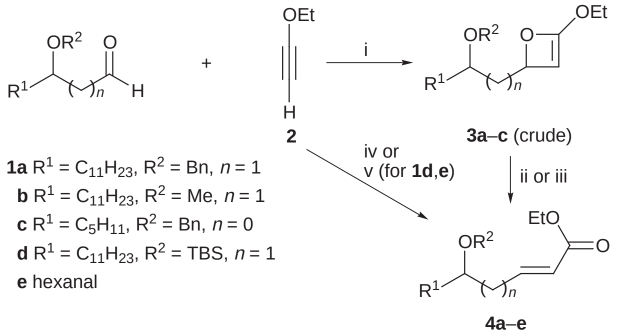
B



C



Further support for this explanation was found in the following experimental results (Table 1). When **2** and **1a** react under BF_3–Et_2O catalysis, the only product we were able to observe is α,β-unsaturated ester **4a** (Table 1, entry 2). Only traces of **3a** were identified during the monitoring of the reaction by TLC. The reaction between **2** and 3-(*tert*-butyldimethylsiloxy)tetradecanal **1d** (R^1 = $C_{11}H_{23}$; R^2 = TBDMS; *n* = 1) or hexanal **1e** under BF_3–Et_2O or $MgBr_2$–Et_2O catalysis leads, in all four cases (Table 1, entries 5–8), to the expected corresponding (*E*)-unsaturated esters **4d,e**. Indeed, in all these cases, the formation of chelates analogous to chelates **A** and



1a R^1 = $C_{11}H_{23}$, R^2 = Bn, *n* = 1
b R^1 = $C_{11}H_{23}$, R^2 = Me, *n* = 1
c R^1 = C_5H_{11}, R^2 = Bn, *n* = 0
d R^1 = $C_{11}H_{23}$, R^2 = TBS, *n* = 1
e hexanal

Scheme 2 *Reagents and conditions*: i, $MgBr_2$–OEt_2 (3 equiv.), CH_2Cl_2, 15 min, −60 °C; ii, BF_3–OEt_2 (cal.), CH_2Cl_2, 1 min, −30 °C; iii, CH_2Cl_2 or $CDCl_3$, 2–3 h, room temp.; iv, BF_3–OEt_2 (1 equiv.), CH_2Cl_2, 30 min, −60 °C; v, $MgBr_2$–OEt_2 (3 equiv.), CH_2Cl_2, 15 min, −60 °C

Table 1 Preparation of oxetes **3a**–**c** and esters **4a**–**e** (yields are unoptimized) from aldehydes **1a**–**e**

Entry	Aldehyde	Lewis acid	Oxete (d.r.)	(*E*)-Ester (yield)
1	**1a**	$\mathrm{MgBr_2}$–$\mathrm{OEt_2}$	**3a** (4 : 1)	**4a** (88%)
2	**1a**	$\mathrm{BF_3}$–$\mathrm{OEt_2}$	—	**4a** (70%)
3	**1b**	$\mathrm{MgBr_2}$–$\mathrm{OEt_2}$	**3b** (9 : 1)	**4b** (67%)
4	**1c**	$\mathrm{MgBr_2}$–$\mathrm{OEt_2}$	**3c** (9 : 1)	**4c** (75%)
5	**1d**	$\mathrm{BF_3}$–$\mathrm{OEt_2}$	—	**4d** (60%)
6	**1d**	$\mathrm{MgBr_2}$–$\mathrm{OEt_2}$	—	**4d** (71%)
7	**1e**	$\mathrm{BF_3}$–$\mathrm{OEt_2}$	—	**4e** (56%)
8	**1e**	$\mathrm{MgBr_2}$–$\mathrm{OEt_2}$	—	**4e** (73%)

therefore **B** is not possible[12] and hence the conrotatory ring opening takes place.

Finally, although **3a–c** are stable in $\mathrm{CDCl_3}$ solution at −20 °C,¶ their life-time at room temperature does not exceed 1 or 2 h and is a few seconds in solution at −30 °C in the presence of $\mathrm{BF_3}$–$\mathrm{Et_2O}$ (in all three cases, ring opening leads to esters **4a**–**c**). This last observation gives further support for the structure of **3a–c** and to our hypothesis of the rigidity of chelate **B**.

In conclusion, we have provided the first evidence of a [2 + 2] mechanism for the studied reaction. We think that the isolation of oxetes **3a–c** at room temperature rests upon the formation of stable chelates **B** which prevents the conrotatory ring opening step of the reaction. Since the formation of **3a–c** occurs with good diasteroselectivity, studies are currently underway to use these as intermediates in synthesis.

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Notes and References

† E-mail: jean-marc.pons@reso.u-3mrs.fr

‡ The structure of **3a** lies upon extensive 2D homo- and hetero-nuclear ^{1}H NMR experiments at 400 MHz. Experimental procedure: a solution of **1a** (0.35 mmol; 111 mg) in $\mathrm{CH_2Cl_2}$ (1 $\mathrm{cm^3}$) was added to a suspension of $\mathrm{MgBr_2}$–$\mathrm{OEt_2}$ (1.05 mmol; 270 mg) in $\mathrm{CH_2Cl_2}$ (3 $\mathrm{cm^3}$) at −60 °C under argon. After 15 min, a solution of **2** (0.70 mmol; 49 mg) in $\mathrm{CH_2Cl_2}$ (2 $\mathrm{cm^3}$) at room temp. was added dropwise to the suspension at −60 °C. TLC monitoring showed the reaction to be completed (no starting material left) after 15 min. The reaction mixture was diluted in light petroleum (10 $\mathrm{cm^3}$) and hydrolyzed with ice–water (2 $\mathrm{cm^3}$). Filtration and concentration *in vacuo* gave 126 mg of crude product; ^{1}H NMR (400 MHz) was used to establish the presence of **3a** as a 4 : 1 mixture of the two diastereomers. An increase in the temperature of the reaction mixture, up to −30 °C, prior to the hydrolysis led to unsaturated ester **4a** (88%). R_f (light petroleum–$\mathrm{Et_2O}$ = 7 : 3) **1a** : 0.5; **3a** : 0.25; **4a** : 0.75.

3a: major isomer: δ_H (400 MHz, $\mathrm{CDCl_3}$) 7.35–7.25 (5 H, m, PhH), 5.12 (1 H, d, *J* 7.9, =CH), 4.60 (1 H, m, CH–O–), 4.59 (1 H, part A of AB system, J_{AB} 11.9, –O–CH_aH–Ph), 4.52 (1 H, part B of AB system, J_{AB} 11.9, –O–CHH_b–Ph), 3.89 (1 H, part A of $\mathrm{ABX_3}$ system, J_{AB} 9.6, J_{AX} 7.1, O–CH_aH–Me), 3.86 (1 H, part B of $\mathrm{ABX_3}$ system, J_{AB} 9.6, J_{AX} 7.0, O–CHH_b–Me), 3.66 (1 H, m, CH–OBn), 1.82 (1 H, part A of ABXY system, J_{AB} 14.5, J_{AX} 8.7, J_{AY} 3.7, O–CH–CH_aH–CH–O), 1.72 (1 H, part B of ABXY system, J_{AB} 14.5, J_{AX} 7.1, J_{AY} 3.3, O–CH–CHH_b–CH–O), 1.88–1.46 (6 H, m), 1.37–1.18 (14 H, m), 0.87 (3 H, t, *J* 7.0, –Me), 0.85 (3 H, br t, O–$\mathrm{CH_2}$–*Me*); δ_c (50.3 MHz, $\mathrm{CDCl_3}$) 138.3 (s), 138.0 (s), 128.5 (d, 2C), 128.0 (d, 2C), 127.9 (d), 111.8 (d), 77.0 (d), 77.1 (t), 68.7 (t), 68.6 (d), 39.8 (t), 33.4 (t), 32.0 (t), 29.8 (t), 29.7 (t, 2C), 29.6 (t, 2C), 29.4 (t), 25.4 (t), 22.8 (t), 14.2 (q, 2C).

§ ^{1}H and ^{13}C NMR data of **3b,c** are similar to those described for **3a**.

¶ Oxete **3c** was, for example, kept over 2 months in a NMR tube (^{1}H concentration). We first imagine that the relative stability of Lewis acid-free **3a** could result from an intramolecular π-stacking (between the double bond and the aromatic ring), but both the formation of **3b** and semiempirical (AM1) calculations were in disagreement with such an explanation.

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