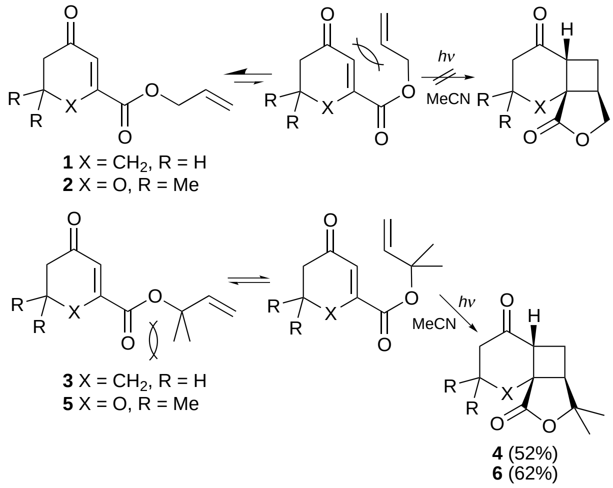
Conformational effects and cyclodimer formation in intramolecular [2 + 2] photocycloadditions

Sylvie Piva-Le Blanc, Jean-Pierre Pete and Olivier Piva*

Unité mixte de recherche CNRS, Université de Reims Champagne Ardenne, BP 1039, 51687 Reims Cedex 2, France

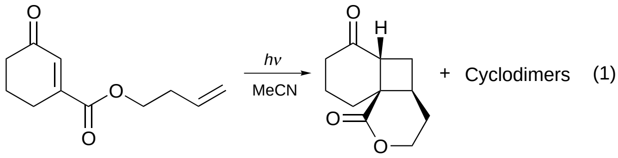
Cyclodimer formation competes with intramolecular [2 + 2] photocycloaddition during the photolysis of ω-alkenyl 3-carboxylatocyclohexenones.

Intramolecular [2 + 2] photocycloadditions are very useful reactions for multistep syntheses of polycyclic molecules.[1] The efficiency of the process depends mainly on the length of the chain between the enone and the alkene moiety and on the strain involved during the cycloaddition process. Intramolecular photocycloadditions can be disfavoured when medium ring cycles would otherwise be formed simultaneously to the formation of cyclobutane. In these cases, hydrogen abstraction[2] or polymerization[3] predominate when conformational restrictions decrease the rate of the intramolecular cycloaddition process. Since they should be good candidates for asymmetric [2 + 2] photocycloadditions,[4] we have studied the reactivity of unsaturated esters of 3-carboxylatocyclohex-2-enone and we now report the unusual effect of the ester linkage on the photocycloaddition process. (Scheme 1).



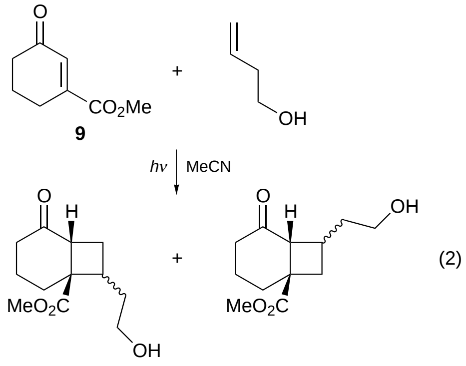
Scheme 1

Intermolecular photocycloadducts could not be isolated from allyl esters **1** or **2** and photodimerization of the enone chromophore (< 5%) was the main reaction observed. The absence of intramolecular photocycloaddition might result from conformational effects as already pointed out by Pirrung and Thomson with other types of carboxylic derivatives.[5] Due to the large preference for an s-*trans* conformation around the CO–O bond of the ester group,[6] the ethylenic bond would be situated too far from the excited enone to allow an intramolecular photocycloaddition process to occur. The conformational origin of the absence of cycloadducts from **1** and **2** was verified by using the *gem*-dimethyl effect.[7] Introduction of two Me groups into the chain of 1,1-dimethylallyl esters **3** and **5** restores its conformational mobility and, as expected, adducts **4** and **6** were isolated in good yields. Use of butenyl esters should minimize the conformational restrictions associated with an ester group and indeed, irradiation at room temperature of butenyl ester **7** (10^{-2} mol l^{-1}) in MeCN or CH_2Cl_2, led to the expected cycloadduct **8** [reaction (1)].[8]



7 | T = 25 °C, T = −55 °C | **8** (67%) (29%) | (10–14%) (45%)

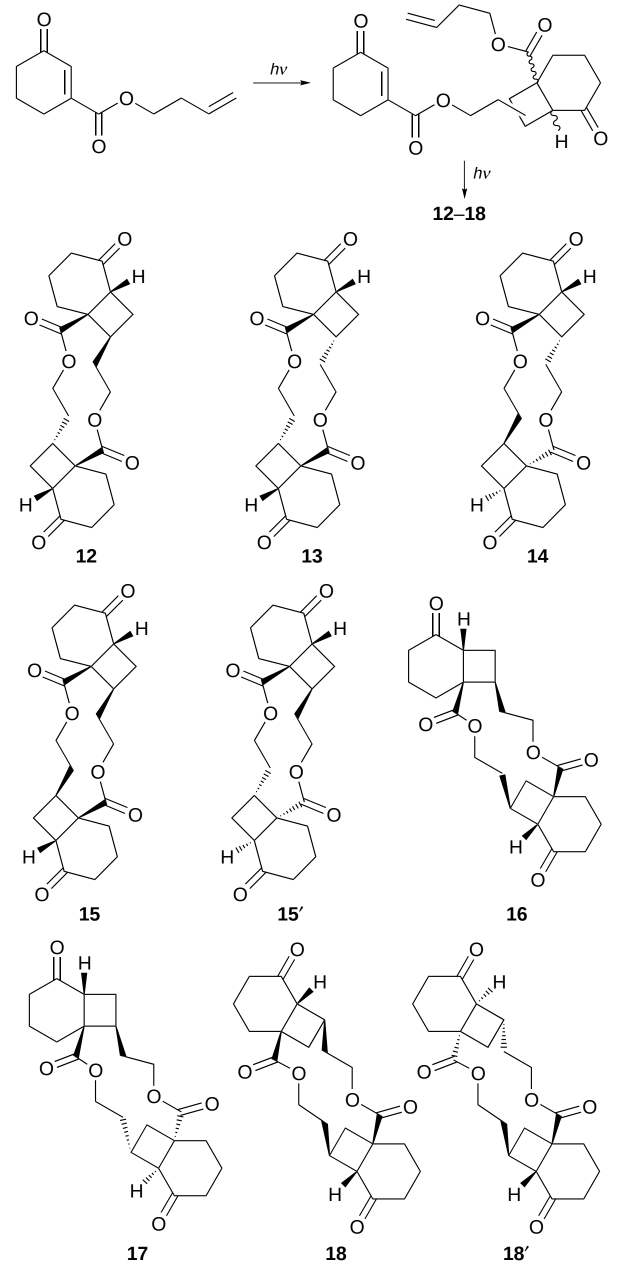
Interestingly, the chemical yield of **8** decreased at low temperatures and a mixture of cyclodimers (up to 45%) was obtained at −55 °C. Analysis of the crude reaction mixture by NMR spectroscopy, at high conversion yields, showed no ethylenic bonds.† Methanolysis of the mixture of oligomers afforded **10** and **11** which were prepared independently by an intermolecular photocycloaddition of oxo ester **9** with but-3-en-1-ol [reaction (2)].



10 50% (*syn*:*anti* 20:30) | **11** 50% (*syn*:*anti* 46:4)

ESMS confirmed the dimeric nature of the isolated oligomers and detected some trimers of the starting material in the reaction mixture. By successive chromatography, crystallization and NMR studies, seven cyclodimers **12–18** were isolated‡ and characterized§ (Scheme 2). Formation of these adducts can be rationalised by a succession of intermolecular and intramolecular photocycloadditions, none of which appeared to be regio- or stereo-selective.[9] In order to increase the yield of macrocyclic structures, we performed the reaction at higher concentration (10^{-1} mol l^{-1}). Unfortunately, photodimerization between the two cyclohexenone moieties was preferred.

To the best of our knowledge, formation of cyclic photodimers has not yet been reported for cycloalkenone derivatives. That an intermolecular process competes with the expected intramolecular cycloaddition probably results from a relatively unfavourable conformation of the substrate. The observed temperature effect might indicate that the reactive conformer for an intramolecular process is more easily accessible at higher temperatures. The unexpected formation of 12-membered ring



Scheme 2

bis-lactones in cyclodimers rather than linear oligomers, in the second photocycloaddition process, indicates that due to steric restrictions, the two reactive entities of the same molecule should be very close in the opened dimer favouring a further intramolecular process.

S. P. L. B. thanks 'Région Champagne-Ardenne' for financial support. We are indebted to Dr T. G. C. Bird (Zeneca Pharma, Reims) for his help with preparing the text of the manuscript.

Footnotes and References

* E-mail: olivier.piva@univ-reims.fr

† Even at conversion yields of about 50% of the starting material, linear photodimers remained very minor compounds in the reaction mixture.

‡ The solvent was first concentrated and the residue dissolved in MeOH. After partial evaporation, macrolide **12** readily crystallized. The MeOH was removed and the mixture chromatographed on silica (eluent: AcOEt–hexanes : 10–60 to 90–40) in order to separate the monomeric lactone **8** and an unseparable fraction of cyclodimers **13**–**18**. The macrocyclic compounds were totally or partially separated using HPLC with a Lichrosorb Si 60-7 column. By NMR analysis of each compound, and by comparison with spectra of the monomeric adduct and also those of compounds **10** and **11**, we were able to attribute the regiochemistry and relative stereochemistry.

§ *Selected data* for **4**: δ_H 1.35 (3 H, s), 1.40 (3 H, s), 1.70–1.90 (1 H, m), 2.00–2.55 (7 H, ma), 2.66 (1 H, td, 7.75, 1.0), 2.74 (1 H, t, 6.7). δ_C 22.35 (q), 22.5 (t), 23.0 (t), 28.7 (q), 28.84 (t), 40.5 (t), 44.0 (d), 46.2 (d), 54.7 (s), 84.2 (s), 179.9 (s), 210.8 (s); $\nu(CHCl_3)/cm^{-1}$ 1755, 1711; *m/z* 208 ($M^{\cdot+}$, 23), 165 (10), 164 (11), 149 (100), 135 (16), 121 (54), 107 (36) (Calc. for $C_{12}H_{16}O_3$: C 69.19; H 7.75. Found C 69.01, H 7.84%). For **8**: δ_H 1.75–1.90 (2 H, m), 1.95–2.27 (5 H, m), 2.32–2.46 (4 H, m), 3.17 (1 H, dd, 11.2, 6.7), 4.31 (1 H, ddd, 18.0, 9.0, 3.0), 4.50 (1 H, ddd, 18.0, 6.7, 3.0); δ_C 19.5 (t), 27.3 (t), 28.8 (t), 31.1 (t), 35.0 (d), 38.5 (t), 44.8 (d), 46.2 (t), 67.1 (t), 175.2 (q), 210.8 (q); $\nu(CHCl_3)/cm^{-1}$ 1720, 1710; *m/z* 176 ($M^{\cdot+}$, 49), 166 (10), 148 (35), 125 (55), 104 (56) (Calc. for $C_{11}H_{14}O_3$: C 68.03; H 7.27. Found C 68.11, H 7.58%). For **12**: δ_H 1.60–2.50 (21 H, m), 2.92 (1 H, dddd, 12.5, 10.3, 8.6, 4.6), 3.16 (1 H, t, 10.1), 3.20 (1 H, dd, 11.5, 5.3), 3.98 (1 H, td, 11.9, 1.1), 4.03–4.14 (3 H, m); δ_C 20.4 (t), 20.9 (t), 24.0 (t), 27.4 (t), 28.9 (t), 29.0 (t), 29.7 (t), 30.6 (t), 34.5 (d), 38.15 (t), 39.5 (t), 42.7 (d), 43.7 (d), 51.0 (s), 52.5 (s), 62.7 (t), 63.3 (t), 174.0 (s), 175.9 (s), 211.2 (s), 212.6 (s); *m/z* 411.96 ($M^{\cdot+}$ Na^+ + H).

1 D. De Keukeleire and S.-L. He, *Chem. Rev.*, 1993, **93**, 359; M. T. Crimmins, *Chem. Rev.*, 1988, **88**, 1453; T. L. Ho, *Carbocycle construction in terpene synthesis*, VCH, Weinheim, 1988.
2 A. Amougay, O. Letsch, J. P. Pete and O. Piva, *Tetrahedron*, 1996, **52**, 2405; C. Meyer, O. Piva and J. P. Pete, *Tetrahedron Lett.*, 1996, **37**, 5885; S. Le Blanc, J. P. Pete and O. Piva, *Tetrahedron Lett.*, 1992, **33**, 1993.
3 F. C. De Schryver, N. Boens and J. Put, *Advances in Photochemistry*, ed. J. N. Pitts, G. S. Hammond and K. Gollnick, Wiley, 1977, vol. 10, 379; B. A. Pearlman, *J. Am. Chem. Soc.*, 1979, **101**, 6398; W. L. Dilling, *Chem. Rev.*, 1983, **83**, 1.
4 J. P. Pete, *Advances in Photochemistry*, ed. D. C. Neckers, D. H. Volman and G. von Bünau, Wiley, 1996, vol. 21, 135.
5 M. C. Pirrung and S. A. Thomson, *Tetrahedron Lett.*, 1986, **27**, 2703.
6 E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of organic compounds*, Wiley, New York, 1994, 618.
7 P. G. Sammes and D. J. Weller, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1205. M. E. Jung and J. Gervay, *J. Am. Chem. Soc.*, 1991, **113**, 224; R. Keese and M. Meyer, *Tetrahedron*, 1993, **49**, 2055; A. L. Parrill and D. P. Dolata, *Tetrahedron Lett.*, 1994, **35**, 7319; M. E. Jung and M. Kiankarini, *J. Org. Chem.*, 1995, **60**, 7013.
8 S. Le Blanc, J. P. Pete and O. Piva, *Tetrahedron Lett.*, 1993, **34**, 635.
9 D. J. Maradyn and A. C. Weedon, *J. Am. Chem. Soc.*, 1995, **117**, 5359.

Received in Liverpool, UK, 29th September 1997; 7/07027F