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Photocycloaddition of (*Z*)-1,2-dichloroethylene to enantiopure 2(5*H*)-furanones: an efficient strategy for the diastereoselective synthesis of cyclobutane and cyclobutene derivatives

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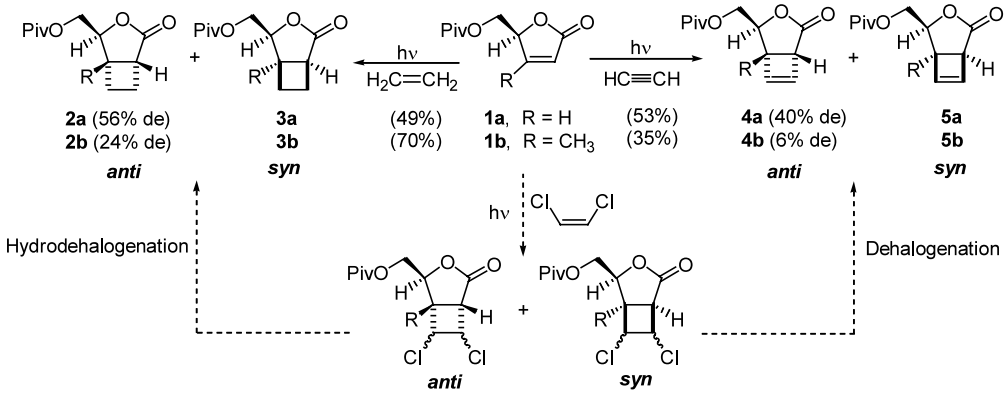
Abstract—A highly stereoselective and efficient synthetic approach to cyclobutane and cyclobutene derivatives has been developed consisting of a [2+2] photochemical cycloaddition of chiral 2(5*H*)-furanones to (*Z*)-1,2-dichloroethylene followed by dihydrodehalogenation or dihaloelimination.

The photochemical [2+2] cycloaddition of olefines and acetylenes to cyclic enones and α,β-unsaturated lactones is a known methodology for the preparation of cyclobutane and cyclobutene compounds.[1] One of the most important aspects for synthetic applications of the above reaction is the control of its stereochemical course.[2] As part of our ongoing research project on developing stereoselective syntheses of natural cyclobutane pheromones,[3] we have studied thoroughly the diastereoselectivity of the photochemical reaction of ethylene and acetylene to homochiral derivatives of (*S*)-5-hydroxymethyl-2(5*H*)-furanones (Scheme 1).[4] Among the studied substrates, the pivaloyl derivative **1a** gave the best facial diastereoselectivity in the photoreaction with ethylene, although the presence of a vinylic methyl group (**1b**) was detrimental for the antifacial selectivity. Moreover, in the photocycloaddition of **1a** and **1b** to acetylene lower stereoselectivities were accomplished. For this reason, and also for the hazardous character of acetylene, we have sought an alternative approach for preparing the target compounds **2** and **4** by a two step protocol consisting of the



Scheme 1.

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use of (*Z*)-1,2-dichloroethylene instead of ethylene or acetylene in the photochemical [2+2] cycloaddition, followed by a reductive treatment of the cycloadducts.[5] Herein we describe preliminary results of our efforts directed to this goal.

The first step of the procedure was the [2+2] photoreaction between lactones **1a**,**b** and (*Z*)-1,2-dichloroethylene. Various solvents were examined,[6] and acetonitrile gave the best yield on the expected dichlorocycloadducts. Thus, 0.018 M solutions of substrates **1a**,**b** with a five molar excess of dichloroethylene in acetonitrile (50 mL or 280 mL) were irradiated through a quartz vessel with a medium pressure 125 W mercury lamp at −20°C. For characterization purposes, the major cycloadducts were isolated by flash column chromatography, but separation was not necessary for further synthetic transformations.

Under the foregoing conditions, the irradiation of lactone **1a** with (*Z*)-1,2-dichloroethylene for 5 h resulted in the formation of a mixture of seven isomeric cycloadducts in the ratio 34:19:15:4:3:24:1 (GC elution order), as evidenced by GC–MS and NMR analysis of the reaction crude, in a combined yield of 89%. The four main stereoisomers **6a**–**9a** (Fig. 1) were isolated and their structures were established by detailed analysis of their ^{1}H and ^{13}C NMR spectra. The value of the coupling constant between H-4 and H-5 is diagnostic for the *anti*/*syn* stereochemistry of the cycloadducts. A small value of $J_{4,5}$ is in agreement with a *trans* relationship between these two protons (*anti* approach), while larger values correspond to a *cis* relationship (*syn* approach).[4a,b] For all compounds **6a**–**9a** the values of $J_{4,5}$ ranged from 0 to 2.9 Hz according to an *anti* stereochemistry, namely the cycloaddition proceed with very high facial discrimination (84%). Relative stereochemistries of the Cl substituents were inferred from the vicinal coupling constants $J_{1,7}$ and $J_{5,6}$.[7] Furthermore, conversion of these adducts into the known compounds **2a** or **4a** (see below) supports the assigned stereochemistry.

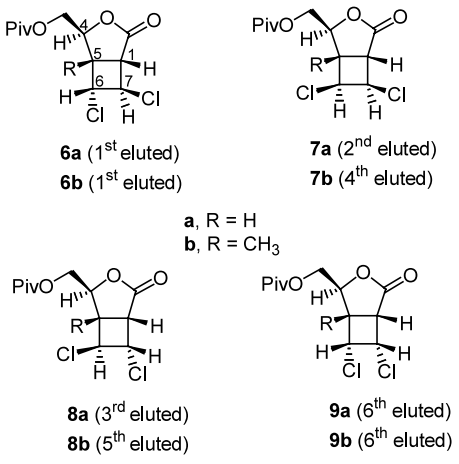


Figure 1.

Encouraged by this excellent result, we explored the analogous photoreaction with butenolide **1b**, that bears a methyl group at the β-position. Thereby, the photocycloaddition of this lactone with (*Z*)-1,2-dichloroethylene afforded the corresponding cycloadducts as a mixture of seven isomers in 34:5:6:11:29:14:1 ratio (GC elution order), according to GC–MS and NMR analysis of the reaction crude, in a combined yield of 87%. The four main adducts **6b**–**9b** were also isolated and analyzed. The *anti*:*syn* arrangement and the relative stereochemistry of the Cl substituents were determined by ^{1}H and ^{13}C NMR, including NOE experiments. The structure of the *trans* dichloro adduct **8b** was confirmed by X-ray diffraction (Fig. 2).[8] As before, the major adducts were assigned as *anti*, indicating that the cycloaddition took place with a remarkable facial selectivity (76%) and further transformations provided additional proof for their stereochemistry.

Since both the yield and the *anti*:*syn* ratio in these reactions were very high, the reductive treatment of the photoreaction mixtures could serve as a very efficient strategy for the diastereoselective synthesis of **2a**,**b** and **4a**,**b** (Scheme 2).

Firstly, we performed the hydrodehalogenation reaction[9] of the mixture of the *anti* and *syn* cycloadducts derived from **1a**. Thus, treatment of this mixture with a four molar excess of tri-*n*-butyltin hydride and AIBN in toluene at 100°C cleanly produced the cyclobutane compounds **2a** and **3a** in 95:5 ratio and 87% yield after purification by flash column chromatography. Similar results came out for the mixture of cycloadducts coming from **1b**. In the event, when this mixture was subjected to the above conditions, both diastereoisomers **2b** and **3b** were obtained in 80% yield in a ratio 90:10. The overall yields of **2a**/**3a** and **2b**/**3b** from lactones **1a** and **1b** were 77 and 70%, respectively. For synthetic purposes, the major cycloadducts can be isolated by flash column chromatography.[4a,b]

Finally, we undertook the reductive elimination of the vicinal dichloride by treating the mixtures of isomers

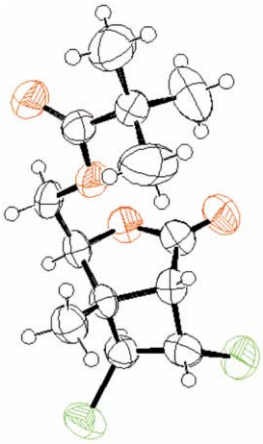
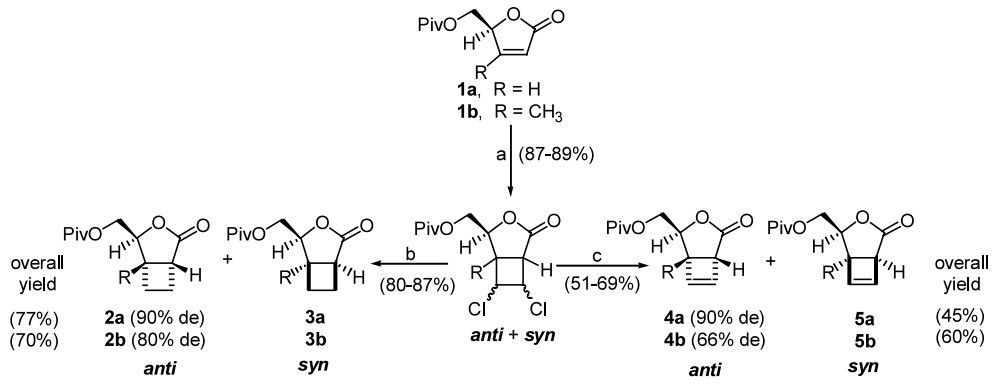


Figure 2. Molecular structure of **8b** (ellipsoids at the 50% level).



Scheme 2. *Reagents and conditions*: (a) *hv*, (*Z*)-1,2-dichloroethylene, acetonitrile, –20°C; (b) *n*-Bu_3SnH, AIBN, toluene, 100°C; (c) Zn, (80%) EtOH, reflux.

with activated zinc. Among the different solvents examined, the best results were obtained in aqueous EtOH.[10] Accordingly, treatment of cycloadducts derived from **1a** with 37 molar equivalents of zinc in refluxing EtOH (80%) for 7 h afforded the cyclobutene compounds **4a** and **5a** in 51% yield and 95:5 ratio. In a similar manner, on submitting the cycloadducts coming from **1b** to the above conditions for 5 h, the diastereoisomeric cyclobutenes **4b** and **5b** were obtained in 69% yield and a ratio 83:17, along with the dichlorocycloadduct **8b** that was resistant to reductive dechlorination. The overall yields of **4a**/**5a** and **4b**/**5b** from lactones **1a** and **1b** were 45 and 60%, respectively. For synthetic purposes, the main cycloadducts can also be isolated by flash column chromatography.[4c]

In summary, we have shown that the photochemical reaction of chiral 2(5*H*)-furanones to (*Z*)-1,2-dichloroethylene afforded the corresponding 1,2-dichloro cycloadducts in excellent yield and antifacial selectivity. The dichlorocycloadducts were used as intermediates for the preparation of cyclobutane and cyclobutene compounds. The overall process represents a convenient and highly diastereoselective methodology for synthesizing such versatile compounds and can be carried out on a multigram scale.

Acknowledgements

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References

1. (a) Owsley, D. C.; Bloomfield, J. J. *J. Chem. Soc. (C)* **1971**, 3445–3447; (b) Kosugi, H.; Sekiguchi, S.; Sekita, R.; Uda, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 520–528; (c) Baldwin, S. W. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1981; Vol. 5, pp. 123–225; (d) Demuth, M.; Mikhail, G. *Synthesis* **1989**, 145–162; (e) Crimmins, M. T. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp. 123–150.
2. (a) Bach, T. *Synthesis* **1998**, 683–703; (b) Hoffmann, N.; Buschmann, H.; Raabe, G.; Scharf, H.-D. *Tetrahedron* **1994**, *50*, 11167–11186.
3. Petschen, I.; Parrilla, A.; Bosch, M. P.; Amela, C.; Botar, A. A.; Camps, F.; Guerrero, A. *Chem. Eur. J.* **1999**, *5*, 3299–3309 and references cited therein.
4. (a) Alibés, R.; Bourdelande, J. L.; Font, J. *Tetrahedron: Asymmetry* **1991**, *2*, 1391–1402; (b) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A.; Parella, T. *Tetrahedron* **1996**, *52*, 1267–1278; (c) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M. *Tetrahedron Lett.* **2001**, *42*, 6695–6697.
5. For a related precedent, see: Cargill, R. L.; Crawford, J. W. *J. Org. Chem.* **1970**, *35*, 356–359.
6. (a) Dilling, W. L.; Tabor, T. E.; Boer, F. P.; North, P. P. *J. Am. Chem. Soc.* **1970**, *92*, 1399–1400; (b) Loufty, R. O.; de Mayo, P. *Can. J. Chem.* **1972**, *50*, 3465–3471; (c) Gauvry, N.; Comoy, C.; Lescop, C.; Huet, F. *Synthesis* **1999**, 574–575.
7. Bongini, A.; Lamartina, L.; Mondelli, R.; Tagliabue, G. *Org. Magn. Reson.* **1975**, *7*, 320–325.
8. Crystallographic data (excluding structure factors) for compound **8b**, has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 196711. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
9. Neumann, W. P. *Synthesis* **1987**, 665–683.
10. Several solvents have been used for reductions with zinc. See for example: (a) Shimo, T.; Somekawa, K.; Kuwakino, J.; Uemura, H.; Kumamoto, S.; Tsuge, O.; Kanemasa, S. *Chem. Lett.* **1984**, 1503–1504; (b) Warrener, R. N.; Pitt, I. G.; Russell, R. A. *Aust. J. Chem.* **1992**, *45*, 1035–1044.