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Stereoselective [2+2] photocycloaddition of acetylene to chiral 2(5*H*)-furanones

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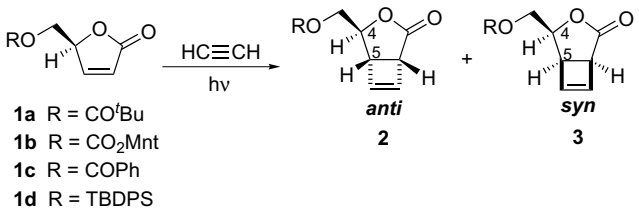
Abstract—The photochemical [2+2] cycloaddition of acetylene to chiral 2(5*H*)-furanones is investigated. The effect of the substituent at the stereogenic center of the lactone on the chemical yield and facial diastereoselectivity is evaluated. Using a C_2-symmetric bis-lactone as substrate, a diastereomeric excess higher than 98% is found. © 2001 Elsevier Science Ltd. All rights reserved.

The [2+2] photocycloaddition of alkenes to cyclic enones and α,β-unsaturated lactones is a well known methodology to obtain cyclobutanic compounds.[1] This reaction has found broad applicability in natural product synthesis.[2] In connection with our ongoing research program on developing diastereoselective synthesis of bio-molecules, we were interested in the stereoselective preparation of chiral polyfunctionalyzed cyclobutene derivatives as precursors to a variety of products with potential biological activity.[3] We envisaged that the photocycloaddition of acetylene to α,β-butenolides could be a convenient approach to such versatile compounds. However, this reaction has received little attention hitherto. Only scattered reports have appeared in the literature[4] and, to the best of our knowledge, chiral versions of such process have not yet been examined. Therefore we decided to investigate thoroughly the photocycloaddition of acetylene to homochiral 2(5*H*)-furanones that should give access to diastereo- and enantiomerically pure four-membered unsaturated rings. Preliminary results of this study are described herein.

Lactones **1a**–**d** were selected as substrates to evaluate the influence of the substituent attached to the stereogenic center on the stereochemical outcome of the photoreaction (Scheme 1). All these lactones were prepared from (*S*)-5-hydroxymethyl-2(5*H*)-furanone[5] by known methodologies.

The pivaloyl derivative **1a** had previously proved quite efficient in inducing facial discrimination on the photocycloaddition to ethylene.[6] In the menthoxycarbonyl derivative **1b**, the bulky group is tethered to the stereogenic center at a longer distance, with the conformational implications that may introduce different steric hindrance in the proximity of the double bond. On the other hand, it was expected that furanones **1c** and **1d**, bearing an aromatic residue, may benefit from a π-stacking interaction with the carbon–carbon double bond of the lactone, shielding one of its faces to the approach of the alkyne.

Substrates **1a**–**d** were irradiated in a solution of acetone or acetonitrile saturated with acetylene in a pyrex or quartz vessel with a medium pressure 125 W mercury lamp at −20°C. The progress of the cycloaddition was carefully monitored by GLC or by ^{1}H NMR analysis and the reaction was quenched at the appropriate time, to avoid as much as possible the formation of by-products. The most significant results of the photochemical reactions are listed in Table 1.



1a R = CO^{t}Bu
1b R = CO_2Mnt
1c R = COPh
1d R = TBDPS

anti
2

syn
3

Scheme 1.

Keywords: photochemical cycloadditions; acetylene; furanones; diastereoselection; cyclobutenes.

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Table 1. Photocycloaddition of lactones **1a–d** to acetylene

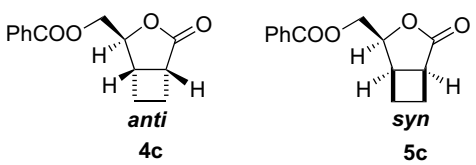
Entry	2(5*H*)-Furanone	R	Solvent	Filter	Time	Yield[a] (%)	**2** *anti*:**3** *syn* (%)
1	**1a**	CO^{t}Bu	Acetone	Pyrex	5.5 h	53	70:30[b]
2	**1b**	CO_2Mnt	Acetone	Pyrex	4.7 h	51	66:34[b]
3	**1c**	COPh	Acetone	Pyrex	3.3 h	26	68:32[c]
4	**1d**	TBDPS	Acetone	Pyrex	6.6 h	–	–
5	**1a**	CO^{t}Bu	Acetonitrile	Quartz	2.5 h	74	66:34[b]
6	**1b**	CO_2Mnt	Acetonitrile	Quartz	2.6 h	57	59:41[b]
7	**1c**	COPh	Acetonitrile	Quartz	40 min	25	66:34[c]
8	**1d**	TBDPS	Acetonitrile	Quartz	3.5 h	–	–

[a] Isolated yields after column chromatography purification (yields refer to the mixture of stereoisomers and are based on % of consumed lactone).
[b] Ratio of isolated products.
[c] These ratios were determined at low conversion of lactone, before formation of **4c** and **5c**.

Under the foregoing conditions, furanones **1a–c** afforded the two expected isomerically substituted 3-oxabicyclo[3.2.0]hept-6-en-2-ones, **2** and **3**, as major products, but **1d** underwent decomposition to unidentified compounds. Both diastereomers were separated by flash column chromatography and their structures were established by detailed analyses of their ^{1}H and ^{13}C NMR spectra. The relative configuration of these cycloadducts could be elucidated considering the value of the coupling constant between H-4 and H-5; the *anti*-isomers **2a–c** showed a small $J_{4,5}$ ($\sim$1.5 Hz), while the *syn*-isomers **3a–c** had a larger $J_{4,5}$ (5.8–7.0 Hz). This stereochemical assignment was confirmed by an X-ray crystal determination for **2b**.[7]

Photocycloadditions performed in acetonitrile were always faster (as evaluated from the time required to achieve similar conversion to products) and, in general, gave better yields than the corresponding reactions in acetone. The low yields of cyclobutenes obtained from furanone **1c** agree with the formation of considerable amounts of the photoreduction by-products **4c** and **5c** (Fig. 1). To characterise these compounds, they were independently prepared by irradiation of **1c** in an acetone solution saturated with ethylene in a 76:24 ratio and 82% overall yield. When cyclobutenes **2a–c** and **3a–c** were irradiated under the same conditions, but in the absence of acetylene, the corresponding cyclobutanes were cleanly formed in all cases. Nevertheless, in the presence of acetylene the photoreduction products of **2a–b** and **3a–b** were not observed. An intramolecular photosensitization caused by the benzoyl moiety in **2**/**3c** may account for this fact.

As was anticipated, the diastereofacial differentiation in the cycloaddition to acetylene was consistent with a preferential approach to the least hindered face of the furanone, giving the *anti*-isomers as major products,



anti **4c** *syn* **5c**

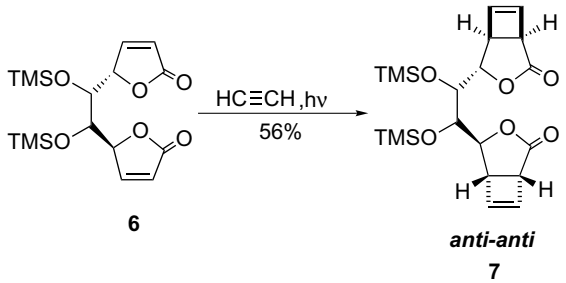
Figure 1.

although efficiency was poorer than that previously found with ethylene.[6] The diastereoselectivity trends observed in both solvents were similar, although the levels of facial discrimination found in acetone were slightly superior. Thus, in the reactions carried out in this solvent the *anti*:*syn* ratio ranges from 66:34 for lactone **1b** (entry 2) up to 70:30 for furanone **1a** (entry 1), while in acetonitrile the *anti*:*syn* ratio increases from 59:41 (entry 6) up to 66:34 (entries 5 and 7). In some [2+2] photocycloadditions of ethylene to several 2(5*H*)-furanones the diastereoselectivity has shown to be dependent on the reaction temperature,[8] but this effect was not detected in the addition to our substrates.[6] Moreover, the use of acetonitrile as solvent precludes the irradiation at lower temperatures due to the increasing solvent viscosity.

It should also be pointed out that significant changes do not exist in the magnitude of the facial selectivities achieved in this series, namely the structural differences between the substituents attached to the stereogenic center are unessential to the diastereoselectivity of the cycloaddition. It seems clear then that the intended π-stacking interaction in furanone **1c** is not at play. Probably, the modest antifacial selectivity is caused exclusively by the higher steric demand of the *syn* face of the lactones, wherein stereoelectronic factors can participate through a favourable n-π overlapping between the lone electron pairs of the oxygen atom of the ester (**1a**, **1c**) or carbonate (**1b**) groups and the π electrons of the butenolide, as previously suggested.[9]

Among the studied derivatives, furanone **1a**, which bears the pivaloyl group, gave the best overall yield (74% in acetonitrile). Despite the moderate diastereoselection, since a simple flash column chromatography provided excellent separation of the two cycloadducts **2a** and **3a**, the described reaction establishes a simple preparative method to synthesise enantio- and diastereomerically pure cyclobutene derivatives which could serve as useful precursors in asymmetric synthesis.

Next we considered the use of C_2-symmetric analogues of **1**, i.e. **6**, as substrates that may enhance the facial selectivity of the cycloaddition process (Scheme 2). Recently, we have prepared several enantiopure bis(α,β-



Scheme 2.

butenolides) and evaluated the influence of the protecting groups of the central diol unit in their [2+2] photocycloaddition to ethylene.[10] An overall antifacial selectivity higher than 98% was achieved with the bis(trimethylsilyl) derivative. Taking into account these previous results, we have performed the cycloaddition of the bis-lactone **6**, synthetically equivalent to **1**, to acetylene.

Thus, the irradiation through a quartz filter of **6** in a solution of acetonitrile saturated with acetylene yielded a crude mixture, whose ^{1}H and ^{13}C NMR spectra showed a main set of signals, diagnostic of a highly symmetric bis(cyclobutene) adduct (diastereomeric excess >98%). The relative configuration of this major cycloadduct was assigned as before by means of the value of the vicinal coupling constant $J_{4,5}$, which is 1.5 Hz, indicating an *anti*:*anti* stereochemistry. Purification by column chromatography allowed us to isolate the cycloadduct **7** in 56% yield.

Therefore, the use of the C_2-symmetric bis(α,β-butenolide) **6** in the photocycloaddition to acetylene has remarkably improved the facial selectivity, affording almost exclusively the *anti*:*anti* isomer **7**. This method provides an efficient and stereoselective approach to densely functionalized bis(cyclobutene) derivatives. Further applications of this chemistry in the synthesis of biologically active compounds are in progress and will be described in due course.

Acknowledgements

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