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Stereoselective Photocycloaddition of Silyl Enol Ethers to Aldehydes. Configurational Control of three Stereogenic Centers in Oxetanes

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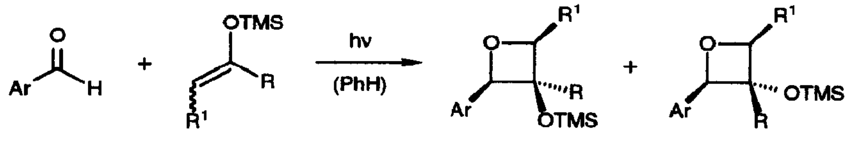
Abstract: The photocycloaddition of unsymmetrically substituted alkenes to an aldehyde leads to eight possible isomeric oxetanes. In sharp contrast to most other substrates, silyl enol ethers **1** which bear a vinylic β-substituent favor only a single stereo- and regioisomer **2** as major product of this reaction.

Oxiranes have gained more importance in modern organic synthesis than any other class of heterocyclic compounds. They are mostly generated by epoxidation of an alkene[1] and can be further utilized by a variety of ring-opening methods.[2] Contrarily, their corresponding homologues the four-membered oxetanes which are commonly prepared by the photocycloaddition of olefins to carbonyl compounds - the so called Paternò-Büchi reaction[3] - have been rarely exploited as synthetic intermediates.[4] Alkenes are precursors for both heterocycles and at first sight the preferential use of oxiranes appears surprising in particular because the C-C-bond forming Paternò-Büchi reaction may be considered synthetically more efficient than an epoxidation. One clue to a possible explanation why oxetanes have been frequently neglected by the chemical community is found in the quest for high selectivity. Whereas oxirane formation occurs stereospecifically from almost any alkene the photocycloaddition of a carbonyl compound is complicated by regio- and stereochemical problems. Indeed, an aldehyde may react with an unsymmetrical alkene to yield eight (2^3) isomeric oxetanes and their enantiomers.[5] The construction of an oxetane ring with distinct geometry, consequently, presents a great challenge to modern methodology.

In search for easy accessible alkenes which can be obtained by a broad range of methods and which may be employed in photochemical oxetane synthesis we have recently found silyl enol ethers as appealing starting materials.[6] We would now like to report on the remarkably stereo- and regioselective Paternò-Büchi reaction of their β-alkylsubstituted derivatives which favors strictly one of the possible eight isomeric oxetanes. The requisite enol ethers **1** were prepared in good yields from the corresponding ketones by kinetically controlled deprotonation (lithium diisopropylamide in THF; -78°C), trapping with chlorotrimethylsilane (TMSCl) and non-aqueous work-up.[7] Irradiation of an aromatic aldehyde in the presence of a comparably small excess of enol ether **1** (1.5-2 equiv.) results in the preferential formation of a single product **2**.[8] Despite the fact that an alkyl substituent R^1 in the vinylic β-position leads to an additional stereogenic center the reaction proceeds even more selectively and with higher yields than the photocycloaddition of β-unsubstituted silyl enol ethers.[6]

Table 1: Photocycloaddition reaction of β-alkylsubstituted silyl enol ethers **1** with aromatic aldehydes [equation (1)] at 30-40 °C in benzene (light source: Rayonet RPR 3000 Å).



1 **2** **3** + other isomers

(1)

entry	Ar	R	R^1	alkene	Z/E (**1**)	time[a] [h]	product	ds[b] [%]	yield[c] [%]
1	Ph	Et	Me	**1a**	25/75	5	**2a**	76[e]	47
2	Ph	Et	Me	**1a**	81/19	8	**2a**	74[e]	35
3	Ph	*i* Pr	Me	**1b**	50/50[d]	6	**2b**	91	69
4	Ph	*t* Bu	Me	**1c**	> 95/5	6	**2c**	> 95	82
5	Ph	Ph	Me	**1d**	> 95/5	48	**2d**	65	53
6	Ph	$CH(OMe)_2$	Me	**1e**	90/10[d]	5	**2e**	92	51
7	Ph	$CEt(OCH_2)_2$	Me	**1f**	> 95/5	5	**2f**	94	67
8	An[f]	$CEt(OCH_2)_2$	Me	**1f**	> 95/5	24	**2g**	> 95	68
9	Ph	*t* Bu	Et	**1g**	> 95/5	5	**2h**	> 95	87
10	An[f]	*t* Bu	Et	**1g**	> 95/5	6	**2i**	> 95	73
11	Ph	*t* Bu	*i* Pr	**1h**	> 95/5	4	**2j**	> 95[g]	84

[a] Length of irradiation. [b] Diastereoselectivities were determined by ^1H-NMR- and GC-analysis of the crude reaction mixture. [c] Isolated yields of the diastereomerically pure product **2** depicted in equation (1). [d] The enol ether mixture contained ca. 5% of the other regioisomer. Although these isomers diminish the yield due to their higher reactivity a separation was not attempted. [e] Traces of two other regioisomeric products were detected by ^1H-NMR analysis. Regioselectivity: 85/15. [f] An = Anisyl (4-Methoxyphenyl). [g] Regioselectivity: 92/8.

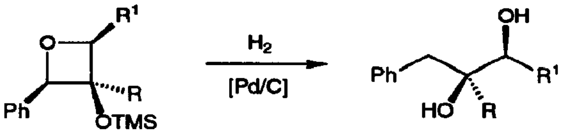
The *E*-/*Z*-geometry of the starting olefin does not influence the product composition. As an example the silyl enol ether **1a** was employed once predominantly in its *E*- (*E*/*Z* = 75/25) and once predominantly in its *Z*-form (*E*/*Z* = 19/81). The isolated major isomer **2a** was identical in both cases and its relative configuration was elucidated by NOE experiments.[9] As depicted in equation (1) the bulky substituents are all oriented *trans* to each other. Although steric bulk in the α-position helps to improve the selectivity decent results are obtained even with simple primary alkyl substituted silyl enol ethers (entry 1).

From a mechanistic point of view, the oxetane formation presumably proceeds stepwise via a triplet biradical intermediate.[10,11] The regioselectivity is determined by the preferential attack of the silyl enol ether's electron rich and less hindered end at the electrophilic aldehyde oxygen to form a stabilized triplet (^3D) biradical. Free rotation allows for the favored *trans*-orientation of β- and α-substituents and therefore accounts for the stereoconvergency mentioned earlier.[12] After intersystem crossing (ISC)[11] the final ring closure step competes with retrocleavage and determines the simple diastereoselectivity as has been extensively discussed elsewhere.[6b]

The assumption of a non-concerted process is supported by the observation that the starting olefins are not configurationally stable in the course of the Paternò-Büchi reaction. Thus, the two different *E*-/*Z*-mixtures of enol ether **1a** which showed no isomerization during irradiation at 300 nm both changed their ratio upon irradiation with the very same light source in the presence of benzaldehyde (*E*/*Z*: from 75/25 to 43/57 and from 19/81 to 34/66 after 6 h). Turro et al. have previously shown in related cases that this behaviour is typical for non-concerted photoreactions via triplet intermediates whereas stereospecific addition without isomerization is indicative for singlet species and a synchronous pathway.[12a]

In general, we have not attempted to isolate any other diastereo- or regioisomer from the reaction mixtures. Mostly GC- and NMR-analyses clearly demonstrated the excellent selectivity of the photocycloaddition. In only one case we noticed a comparably low diastereoselectivity which was preponderantly due to a single second stereoisomer (entry 5).[13] Its isolation and subsequent analysis revealed that this particular oxetane possesses a configuration in which all bulky substituents are located *cis* to each other [cf. equation (1)]. Although the suggestion is merely speculative a change in mechanism may account for the occurrence of **3d**. Since aryl substituted silyl enol ethers are photoactive at 300 nm as indicated by the rapid *E*-/*Z*-isomerization of **1d** at this wavelength it is tempting to make the different chromophore and its consecutive reaction pathways responsible for the formation of **3d**. Nonetheless it remains unclear why only a single stereoisomer has been formed as side product and our work in this area will continue.

The oxetanes obtained are useful building blocks for further functionalization. An important aspect in this context is the question of regioselective ring opening. We have already shown for C(4)-unsubstituted oxetanes that cleavage of the C(2)-O bond by catalytic hydrogenation proceeds cleanly in almost quantitative yield.[14] Identical behaviour was expected for **2** as potential substrates and has already been demonstrated in several instances [equation (2)].



2a-2f **4a-4f** (83-98 %) (2)

The photocycloaddition-hydrogenation reaction outlined above serves as a high yielding method for the carbohydroxylation of silyl enol ethers. Still, we are aware that the C(4)-O bond cleavage may be of even greater interest to synthetic chemistry. The Paternò-Büchi reaction under scrutiny fascilitates the stereoselective construction of a hindered and difficult to form C-C bond and the relative configuration at this site ought to be preserved. Known methods which have been applied to the ring opening of less complicated oxetanes have failed in our case and we have therefore launched a program to study this problem. Results of this endeavour and applications to synthesis will be reported in due course.

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9. A more extensive discussion of the structure elucidation, including NOE studies on **2a**, **2d** and **3d** and X-ray data of **2c**, will appear: Bach, T.; Grehl, M.; Fröhlich, R. manuscript in preparation.
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13. Selected data of **2d**: ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = -0.55$ [s, 9 H, Si(C*H*$_3$)$_3$], 1.58 (d, $^3J = 6.2$ Hz, 3 H, C*H*$_3$), 5.25 (q, $^3J = 6.2$ Hz, 1 H, C*H*CH$_3$), 6.04 (s, 1 H, C*H*Ph), 7.21-7.48 (m, 8 H, arom. H), 7.55-7.63 (m, 2 H, arom. H). - ^{13}C NMR (CDCl$_3$, 75.5 MHz): $\delta = 1.0$ [q, Si(*C*H$_3$)$_3$], 16.2 (q, *C*H$_3$), 82.2 (s, *C*OTMS), 84.5 (d, *C*HCH$_3$), 89.0 (d, *C*HPh), 127.0 (d, C_{ar}H), 127.7 (d, C_{ar}H), 128.1 (d, C_{ar}H), 128.2 (d, C_{ar}H), 128.5 (d, C_{ar}H), 128.6 (d, C_{ar}H), 137.7 (s, C_{ar}), 143.1 (s, C_{ar}).

    3d: ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 0.30$ [s, 9 H, Si(C*H*$_3$)$_3$], 1.18 (d, $^3J = 6.4$ Hz, 3 H, C*H*$_3$), 5.32 (q, $^3J = 6.4$ Hz, 1 H, C*H*CH$_3$), 6.06 (s, 1 H, C*H*Ph), 7.05-7.32 (m, 10 H, arom. H). - ^{13}C NMR (CDCl$_3$, 75.5 MHz): $\delta = 2.2$ [q, Si(*C*H$_3$)$_3$], 16.3 (q, *C*H$_3$), 84.0 (s, *C*OTMS), 86.8 (d, *C*HCH$_3$), 91.1 (d, *C*HPh), 124.9 (d, C_{ar}H), 126.7 (d, C_{ar}H), 126.8 (d, C_{ar}H), 126.9 (d, C_{ar}H), 127.4 (d, C_{ar}H), 128.5 (d, C_{ar}H), 137.5 (s, C_{ar}), 138.3 (s, C_{ar}).
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