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STEREOSELECTIVE SYNTHESIS OF UNSATURATED OXETANES

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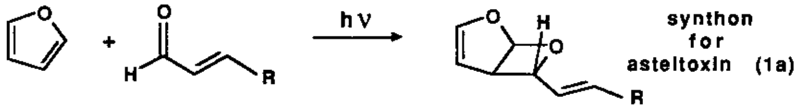
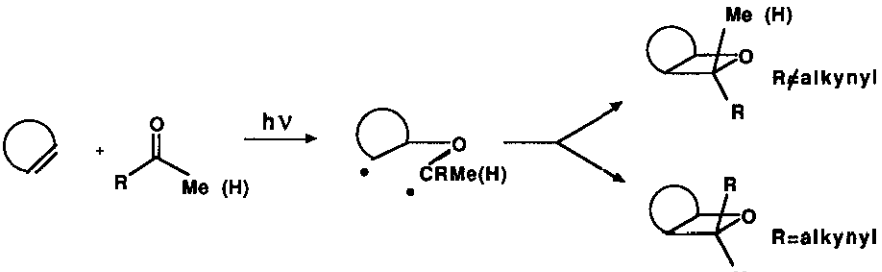
Abstract — *Butynones 1 and 7 add on alkenes under UV irradiation to afford α-alkynyloxetanes. The oxetanes obtained with cyclic alkenes have been shown to have the triple bond endo. Adducts with furan have been converted to an α-vinyloxetane 6 having the double bond endo.*

The Paterno-Buchi reaction has been well documented for its synthetic[1] and mechanistic[2] implications. For instance, addition of carbonyl compounds on alkenes gives oxetanes, which have been used as synthons for natural product synthesis[1] (Equation 1).



Equation 1

The stereoselectivity of these reactions is usually high: the major oxetane is always the least hindered isomer, as a result of minimization of the steric interactions in the intermediate biradical[2,3]. Thus, reaction of an aldehyde or a methyl ketone on a cyclic alkene leads with high stereoselectivity to bicyclic oxetanes having the hydrogen or the methyl group endo (Scheme 1). With 3-alkyn-2-ones, a different stereoselectivity can be expected: the major oxetane should now be the isomer having an endo R chain. Because of the very small sterical requirement of the triple bond[4], the methyl group is now expected



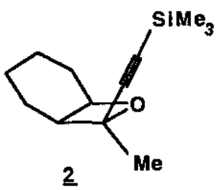
Scheme 1

to be the more bulky substituent and to occupy the exo position (Scheme I). Subsequent chemical modifications from the triple bond should thus provide access to new functionalized oxetanes, with a stereochemistry which is not accessible by another route. It is very surprising to note that this stereochemical study has never been envisaged in the reports dealing with synthesis of alkynyloxetanes[5]. In this paper, we report a stereochemical study of [2+2] cycloaddition of 4-trimethylsilyl-3-butyn-2-one 1[6] onto alkenes.

Preparation of oxetanes

The results of preparative experiments are reported in Table 1. The ynone 1 reacted with cyclohexene and furan and gave the expected oxetanes 2, 3a and 3b, as the major products isolated from the reaction mixture. Similarly, tetramethylethylene yields 4 as the only product of the reaction, besides polymeric material. In contrast, no oxetane was isolated from dihydropyran cycloaddition.

Alkene	Concentration (M)	Irradiation time (hours)	Solvent	Temperature (°C)	Oxetane	Yield (%)
cyclohexene	6.5	91	hexane	-15	2	17
furan	0.8	97	cyclohexane	-30	3a 3b	23 4
tetramethyl ethylene	0.8	97	hexane	-30	4	21
dihydro pyran	0.8	97	hexane	-30	-	-



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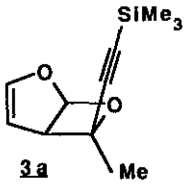

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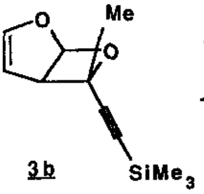

3b

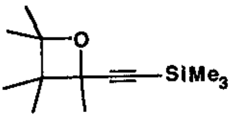

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Table 1: Irradiation of Alkynone 1 (0.15 M) with Alkenes
(The yields refer to isolated and purified oxetanes)

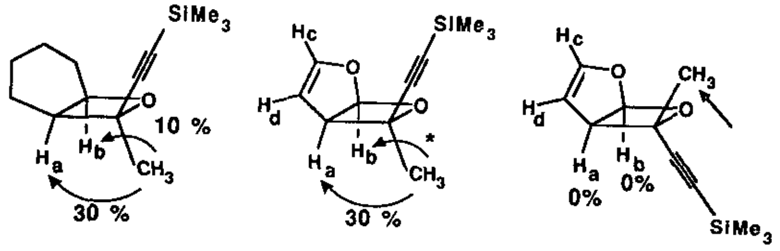
The structures of the oxetanes were established by spectroscopic techniques, and were consistent with literature data[1,3,5,7,18]: the C-O-C vibration band appears as the strongest band in the infrared spectrum around 980 cm^{-1} whereas the typical resonances of the ring protons and carbons were present in the nmr spectra (see Table 2). All the assignments were confirmed by decoupling and COSY techniques. Reaction of ynone 1 with furan leads to a mixture of two isomers 3a and 3b which were separated by preparative thin layer chromatography (Table 1). With cyclohexene, a single oxetane was detected in the crude reaction mixture by spectroscopic of chromatographic technniques. Nevertheless, products resulting from hydrogen abstraction processes were isolated[8a].

With dihydropyran, hydrogen abstraction processes became so efficient that oxetane formation could not compete anymore. With cyclohexene, we also isolated in 7% yield 9-trimethylsilylnon-6-en-8-ynal, resulting from olefin metathesis[8b,c].

Despite the moderate yield in isolated products, the reactions are convenient for the preparation of oxetanes 2-4, since several grams can be obtained from a single irradiation on a 500 ml scale, because of the high concentration of the reactants and the easy separation of the products. Furthermore, these reactants are cheap, or easily accessible. The crude reaction mixtures can be used for further reactions[1b].

Stereochemistry of the oxetanes

Determination of the stereochemistry of cyclic compounds is usually achieved with help of nmr spectra. But in contrast to six-membered ring compounds, coupling constants are of little help for oxetanes, since the difference between the coupling constants Jcis and Jtrans of vicinal protons is often too small to be reliable[9,10]. Other methods, like determination of pseudo-contact shifts[3,11] or analysis of the shielding of ring protons by methyl groups[12], are best used when all stereoisomers are available, and that was not the case with 2[13]. The stereochemistries of 2, 3a and 3b were determined using nuclear Overhauser effect (nOe)[14].



2 3a 3b

Scheme 2: Nuclear Overhauser Effect on Alkynyloxetanes

Oxetanes 2, 3a and 3b were very suitable for this technique, because of their sharp methyl signal. We had to find out solvent conditions where the Ha resonance (Scheme 2) was as far away as possible from the irradiated methyl group. This was best achieved using CD_2Cl_2 for 2 and C_6D_6 for 3a and 3b. Irradiation of the methyl resonances resulted in a strong exaltation (30%) of the intensity of the signals of ring protons Ha of 2 and 3a (Scheme 2). The effect on Hb was much smaller: 10% for Hb of 2 ; for 3a, the change in signal area was too small as compared with the accuracy of the integration technique, and in that case, we used pulsed nmr to confirm the nOe. Figure 1 shows the computed difference between the spectra obtained with and without irradiation of the methyl at 1.56 ppm ; the strong positive nOe on Ha (at 3.10 ppm) is confirmed ; there is also a net effect on Hb (at 5.90 ppm), although it is much smaller than for Ha. In contrast, no effect could be detected on the protons of isomer 3b, neither by continuous wave nor by pulsed nmr techniques.

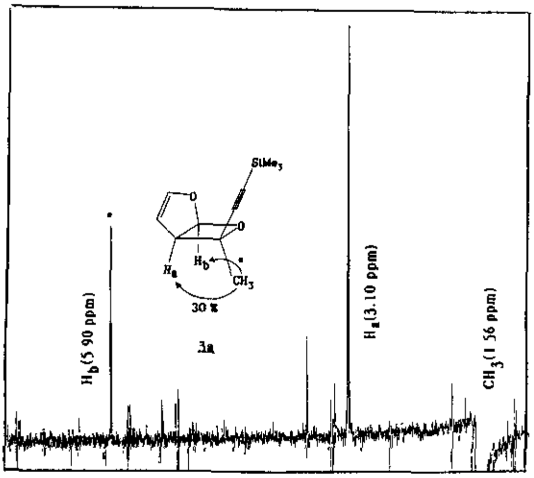


Figure 1 : Computed NOE on Oxetane 3a

These results are consistent with the stereochemistries shown in Scheme 2 for 2, 3a and 3b: the oxetanes 2 and 3a have their methyl group on the same side of the four-membered ring than Ha and Hb, their ring junction is thus cis, and their alkynyl group is endo. The minor oxetane 3b has its methyl group too remote from Ha and Hb to influence them, and its alkynyl group is thus exo[13].

The knowledge of the stereochemistries allows explanation of the large differences observed in the nmr spectra of our oxetanes (*Table 2*): *it appears that the anisotropy of the triple bond has little effect, and* that the major factors influencing the chemical shifts are methyl anisotropy for ring protons[12] and γ-gauche effects for carbons[15] bound to the four-membered ring.

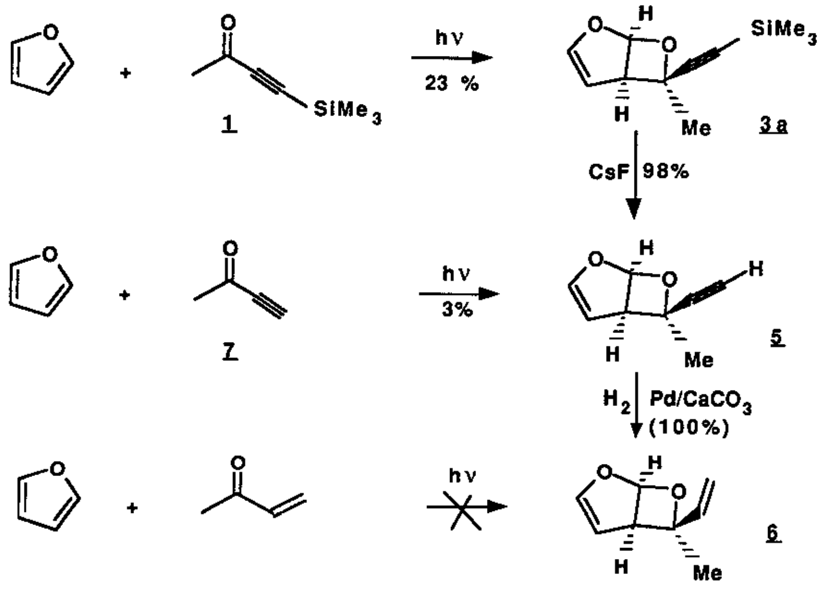
	Proton NMR				Carbon NMR	
	Ha	Hb	Hc	Hd	Me	CCTMS
3a	3.10	5.90	6.40	5.10	29.91	105.04
3b	3.65	6.20	6.20	4.56	24.58	108.73

Table 2: Chemical Shifts of Protons and Carbons of 3a and 3b in C_6D_6 (in ppm)

The Paterno-Buchi reaction of α-alkynyl ketone 1 thus appears to proceed with a good stereoselectivity, giving, as we expected, the triple bond endo. It seemed thus possible, starting from α-alkynyl oxetanes, to prepare new oxetanes possessing the more bulky group endo. To check this possibility, we explored the access to vinyloxetane 6 from 3a.

Synthesis of vinyloxetane 6

Vinyl- or alkenyloxetanes are usually not obtained by photoaddition of enones on alkenes[1c,16,17]. Whereas the Paterno-Buchi reaction is compatible with the presence of several unsaturated groups conjugated with the reactive carbonyl, such as an aryl[3], an other carbonyl[18], or an alkynyl[5], alkenyloxetanes can only be obtained from conjugated enals[1a-c,3], from cyclopentenones and cyclohexenones[19], but not from acyclic enones[1c,16a].



Scheme 3

Attempts to reduce the triple bond of 3a by red-Al or by catalytic hydrogenation resulted only in cleavage of the four-membered ring. We felt that this situation might be the result of steric hindrance of the trimethylsilyl group, and we converted 3a to 5 in 98% yield with Cesium fluoride[14].

The oxetane 5 was also obtained in low yield by photoaddition of butynone 7 on furan, as an only oxetane (Scheme 3). Unfortunately, this reaction leads to extensive polymerization, resulting even in a deposit of solid on the walls of the reaction vessel. The chemical correlation between oxetanes 3a and 5 shows that ynone 7 exhibits the same stereoselectivity than ynone 1.

The monosubstituted triple bond of 5 was then smoothly hydrogenated in the presence of Lindlar catalyst^{16a}, giving the vinyloxetane 6 in almost quantitative yield. This reactional sequence shows that 6 has the vinyl group endo. An attempt to prepare 6 from 3-buten-2-one with furan failed, illustrating the interest of alkynyloxetanes to synthetize alkenyloxetanes.

Generalization of the preparation of the vinyloxetanes, and examination of the reactivity of these compounds are now in progress.

EXPERIMENTAL

Nmr spectra were recorded on BRUKER WP 80 (for determination of Nuclear Overhauser Effect) and WP 300 instruments. Chemical shifts are in ppm, relative to TMS. Ir spectra were obtained with a PHILIPS SP 2000 spectrometer, and the frequencies are given in cm^{-1}. Irradiations were performed with a PHILIPS HOQ 400 W lamp, using pyrex filters ($\lambda > 300$ nm), immersed in a cooled bath.

Ynones 1 and 7 were obtained following references^{6} and ^{20} respectively. The alkenes and solvents were purchased from ALDRICH Chemicals, and distilled over sodium-benzophenone reagent prior to use.

General Procedure for Irradiations: the solution containing the reactants was placed in a dry Schlenck tube, deoxygenated by Argon, immersed in a cooled bath of ethanol (the temperatures are reported in Table 1). Progress of the reaction was monitored by infrared spectroscopy: the irradiation was carried on until the initial intensity of the C=O vibration band was reduced of at least 90%.

The solvent and excess alkene were then removed at room temperature under 14 mm vacuum and trapped at liquid nitrogen temperature. The residue was then separated by preparative thin layer chromatography, which afforded better yields than column chromatography. Oxetanes are usually unstable compounds and can be stored in a freezer for a few weeks.

7-Methyl-7-(2-Trimethylsilylethynyl)-8-oxabicyclo[4.2.0]octane 2: isolated from 2.32 g of 1 (see Table 1) ; mobile phase: ethyl acetate (5%) in pentane. H-nmr (CD$_2$Cl$_2$): 4.64 (1-H, ddd, J=7.4, 5.6 and 4 Hz), 2.52 (6-H, ddd, J=8.6, 7.4 and 5.2 Hz), 1.93 (1H, dddd, J=5.3, 5.3, 8.9 and 14.2 Hz), 1.85-1.50 (5H, m), 1.55 (3H, s), 1.35-1.10 (2H, m), 0.10 (9H, s). C-Nmr (C$_6$D$_6$) : 108.18 (s, 7-C), 93.05 (s, 7'-C), 79.40 (s, 7"-C), 74.31 (d, 1-C), 42.02 (d, 6-C), 29.64 (q, 7-Me), 29.64 (t), 23.61 (t), 21.48 (t), 19.71 (t), 0.43 (q). Ir (CHCl$_3$): 3010, 2950, 2870, 2660, 1450, 1370, 1250, 1240, 1100, 940, 900, 860, 840. Mass m/z 222 (1%), 207 (5), 179 (3), 151 (10), 142, 141 (100), 101, 99, 83, 82, 75, 73, 67, 59, 54. Hrms: calc. for C$_{13}$H$_{22}$OSi: 222.1440 ; found: 222.1452.

9-Trimethylsily-6-Nonen-8-Ynal: H-nmr (CDCl$_3$): 9.75 (1H, t, J=7.15 Hz), 5.67 (dt, J=1.5 and 7.5 Hz), 2.30 (2H, dt, J=1.5 and 7.5 Hz), 1.80 (3H, d, J=1.5 Hz), 1.90-1.30 (6H, m), 0.20 (9H, s). Ir (CHCl$_3$): 3030, 2970, 2880, 2150, 1730, 1650, 1460, 1250, 950, 840. Mass: m/z = 222, 207, 142, 141 (100%), 123, 117, 105, 101, 99, 97, 83, 75, 73, 67, 59. Hrms: calc. for C$_{13}$H$_{22}$OSi: 222.1440 ; found: 222.1459.

6-Methyl-6-(2-Trimethylsilylethynyl)-2,7-dioxabicyclo[3.2.0]hept-3-ene 3a: isolated from 4.2 g of 1 by destillation under vacuum (0.0002 mm Hg), and then separated from 3b by chromatography (mobile phase: 10% ethyl acetate in pentane) ; mp: 35°C ; H-nmr (C$_6$D$_6$): 6.40 (3-H, m), 5.90 (1-H, dd, J=1 and 4 Hz), 5.10 (4-H, t, J=3 Hz), 3.10 (5-H, m), 1.56 (3H, s), 0.17 (9H, s). C-nmr (C$_6$D$_6$): 148.71 (d, 3-C), 105.59 (s, 6-C), 105.04 (d, 1-C), 103.07 (d, 4-C), 91.78 (s, 6'-C), 84.38 (s), 55.27 (d, 5-C), 29.91 (q, 6-Me), -0.16 (q). Ir (CHCl$_3$): 3000, 2170, 1610, 1450, 1375, 1280, 1260, 1250, 1230, 1200, 1130, 1080, 1045, 1020, 980, 950, 900, 850, 820. Mass: m/z = 208 (1%), 193, 165, 125, 109, 97, 91, 83, 73, 68 (100%). Hrms : calc for C$_{11}$H$_{16}$O$_2$Si: 208.0918, found: 208.0906.

3b : oily ; H-nmr (C_6D_6) : 6.20 (1-H and 3-H, m), 4.56 (4-H, t, J=3 Hz), 3.65 (5-H, m), 1.51 (6-Me), 0.21 (9H, s). C-nmr (C_6D_6) : 149.57 (d, 1-C), 108.73 (s, 6-C), 105.72 (d, 1-C), 100.38 (d, 4-C), 90.80 (s), 82.80 (s), 56.02 (d, 5-C), 24.58 (q, 6-Me), 0.16 (q). Ir ($CHCl_3$) : 3000, 2170, 1605, 1450, 1370, 1280, 1260, 1250, 1155, 1130, 1095, 1045, 1015, 975, 940, 900, 850, 825. Mass : m/z = 208, 193, 165, 125, 109, 97, 91, 83, 73, 68.

2,3,3,4,4-Pentamethyl-2-(2-trimethylsilylethynyl)oxetane 4 : isolated from 4.2 g of 1 in 21% yield. This oxetane was chromatographed with ethyl acetate (10%) in light petroleum as mobile phase. Oily ; H-nmr (C_6D_6) : 1.52 (s, 3H), 1.46 (s, 3H), 1.27 (s, 3H), 1.14 (s, 3H), 0.96 (s, 3H), 0.18 (s, 9H). C-nmr (C_6D_6) : 109.73 (s, 2-C), 90.98 (s), 84.54 (s), 79.32 (s, 4-C), 44.02 (s, 3-C), 26.12 (q), 26.05 (q), 25.71 (q), 22.44 (q), 19.77 (q), 0.01 (q). Ir (CCl_4 : 3000, 2980, 2170, 1470, 1390, 1370, 1250, 1215, 1150, 1135, 1110, 1070, 935, 850, 840. Mass : m/z = 224 (3%), 209, 166, 151 (31%), 84 (100%), 83, 75, 73, 69, 59. Hrms : calc. for $C_{13}H_{24}OSi$: 224.1594, found : 224.1582.

Desilylation of Oxetane 3a : a solution of 3a (100 mg) in acetonitrile (5 ml) was added under an atmosphere of Argon to dry Cesium fluoride (75 mg). After stirring at room temperature for 2 h, a new compound was obtained in quantitative yield. It was isolated by filtration followed by evaporation of the solvent : 6-ethynyl-6-methyl-2,7-dioxabicyclo[3.2.0]hept-3-ene 5 : H-nmr ($CDCl_3$) : 6.67 (3-H, m), 6.20 (1-H, dd, J=4.25 and 0.75 Hz), 5.35 (4-H, dd, J=3 and 3 Hz), 3.75 (5-H, ddd, J=4.25, 3 and 1.25 Hz), 2.70 (1H, s), 1.85 (3H, s). Ir ($CHCl_3$) : 3310, 3030, 2990, 2940, 1605, 1450, 1370, 1275, 1230-1200, 1130, 1075, 1045, 1020, 980, 955, 930, 900, 860, 845, 820, 640. Mass : m/z = 136 (2%), 119, 118, 107, 79, 77, 69, 68 (100%), 57, 53, 51.

Irradiation of Butynone 6 with Furan : 6 (204 mg) was irradiated for 97 h at -30°C in a mixture of furan (1.1 ml) and hexane (20 ml). The H-nmr spectrum of the crude reaction mixture shows the presence of two oxetanes in a ratio of 9:1. The major isomer was isolated by thin layer chromatography, and was identified to 5 by its chromatographic and spectroscopic properties.

Hydrogenation of Oxetane 5 : 5 (150 mg) was stirred with Lindlar catalyst (25 mg), quinoline (6.5 mg) in THF (5 ml), in Hydrogen atmosphere. After uptake of 1 equivalent of Hydrogen, the crude reaction mixture was filtered on celite, the solvent was evaporated, and the oxetane 6 was isolated by thin layer chromatography.

6-Vinyl-6-methyl-2,7-dioxabicyclo[3.2.0]hept-3-ene 6 : oily ; H-nmr ($CDCl_3$) : 6.50 (3-H, m), 6.20 (1-H, dd, J=5 and 1 Hz), 5.90 (6a-H, dd, J=10 and 17 Hz), 5.20 (6b-H, dd, J=17 and 2 Hz), 5.10 (6b-H, dd, J=10 and 2 Hz), 4.98 (4-H, t, J=3 Hz), 3.70 (5-H, m), 1.62 (3H, s). Ir (CCl_4) : 3050, 1740, 1610, 1380, 1260, 1130, 1045, 985, 930, 815.

Nuclear Overhauser Effect Experiments : the oxetanes (12 mg) were dissolved in the appropriate solvent (0.9 ml) and the solution was degassed by three freeze-and-pump cycles, before the nmr tube was sealed. The values indicated in scheme 2 are the average obtained from 10 experiments.

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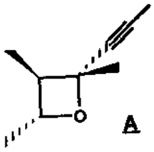
13. The Paterno-Büchi addition of pent-3-ynone on but-2(E)-ene leads to a major oxetane to which the authors attributed structure A on the basis of the methyl shielding effects on the chemical shifts of the ring protons^{5a}. But structure B, which would be in better agreement with our results, since it has the triple bond on the most hindered side, is also consistent with the reported nmr data^{5a}.



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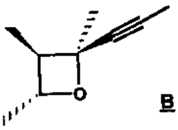

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