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Preparation of 2-Alkylidene Oxetanes: An Investigation of the Paterno-Büchi Reaction Between Aliphatic Aldehydes and Allenes

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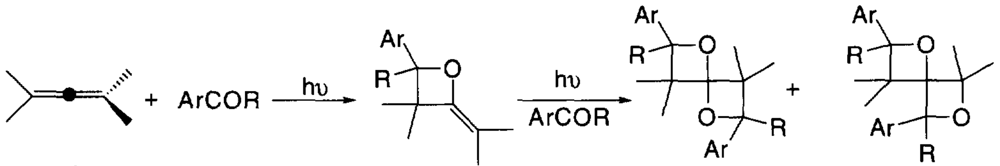
Abstract: Preliminary results of an examination of factors influencing the stoichiometry and regioselectivity of the Paterno-Büchi reaction between aliphatic aldehydes and nonsymmetrical allenes are divulged. Surprisingly little regioselectivity was seen with 3-methyl-1,2-butadiene (**6**); however, 1-ethoxy-1,2-propadiene (**14**) provided a single regioisomer.Copyright © 1996 Elsevier Science Ltd

2-Alkylidene oxetanes **1** are a class of compounds that offers a unique combination of functionalities--a reactive oxetane, an enol cyclic ether and an exocyclic double bond--suggesting intriguing possibilities for their further manipulation. Obviously, ready access to these compounds is necessary for an exploration of their reactivity and utility. The preparation of 2-alkylidene oxetanes has received little attention in the chemical literature,[2-6] with most examples resulting from a [2 + 2] photochemical (Paterno-Büchi) cycloaddition between aromatic carbonyl compounds **2** and tetramethylallene (**3**).[2,3] Although yields of photoadducts were reasonable, the major products often resulted from *bis*-addition of the carbonyl compounds to give dioxaspiroheptanes **4** and **5**, in spite of using a large excess of allene. Beyond noting that for 1:1 adducts the oxygen became, without exception, bonded to the central sp allenic carbon atom, no systematic investigation of factors that govern the stoichiometry, regioselectivity and stereoselectivity of the cycloaddition reaction has been undertaken.

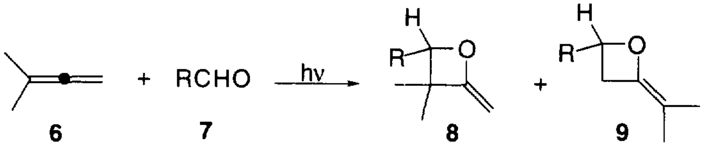


3 **2** **1** **4** **5**

We believe that using the Paterno-Büchi reaction for the synthesis of 2-alkylidene oxetanes is attractive because of the ready availability of aldehydes, ketones and allenes, because of the atom economy[7] of the transformation and as an illustration of an environmentally benign process in those cases where the reaction can be run in the absence of solvent. In this communication we report the results of a preliminary investigation of the Paterno-Büchi reaction between simple aliphatic aldehydes and a range of allenes. We were particularly interested in aliphatic aldehydes because we felt that the resultant products would be, on the whole, more useful as synthetic intermediates. Also, aliphatic aldehydes often undergo the Paterno-Büchi reaction via the singlet manifold, which is generally more stereoselective than the triplet manifold of aromatic carbonyl compounds.[8] The issue of stereoselectivity is of obvious importance, especially because the allenic moiety is chiral if appropriately substituted. In addition to our interest in aliphatic aldehydes, we wanted to examine the regioselectivity of the Paterno-Büchi reaction with nonsymmetrical allenes. Although we studied a variety of nonsymmetrical allenes, the one employed for the initial experiments was 3-methyl-1,2-butadiene (**6**) (dimethylallene) because of its commercial availability.

For the photochemical reactions the allene **6** (7.35 mmol) and aldehydes **7** (1.83 mmol) were combined in a Pyrex tube (medium wall, 13 mm od), degassed through 3 freeze/thaw cycles then flushed with nitrogen. The tube was sealed with a Teflon tap and placed next to a cooling jacket surrounding a Hanovia lamp and irradiated until the aldehyde was consumed (based on ^{1}H NMR--24-48 h). The major products, 2-alkylidene oxetanes **8** and **9**,[9] were isolated by chromatography on flash silica that had been deactivated with triethylamine.[10] The results are shown in the Table.

Table

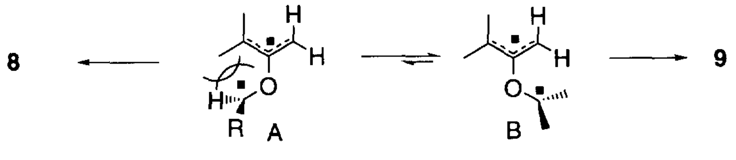


Entry	7 (R=)	Ratio **8**:**9**^{a}	Yield of **8** + **9**^{b} (^{c})^d
1	CH_3CH_2	2:1	69 (30)
2	$(CH_3)_2CHCH_2$	2:1	66 (35)
3	$(CH_3)_2CH$	1:1	54 (25)
4	$(CH_3)_3C$	1:1	38 (20)

Notes: a. Ratios are based on GC analyses of at least three experiments, using a 4 fold excess of allene; b. Yields are GC yields, averaged from at least three experiments after consumption of aldehyde (24-48h); c. Isolated yields are in parentheses; d. We have made the observation that product volatility is an issue with 2-alkylidene oxetanes formed from simple aliphatic aldehydes and allenes, and, therefore, these isolated yields should be considered as nonoptimized.

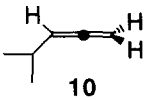
There are several points about the photochemical reactions between the aldehydes and dimethyallene (**6**) that require elaboration. Successful intermolecular Paterno-Büchi reactions are, in general, conducted with a fairly large excess of alkene. Although, theoretically, one could recover unreacted allene, it would be more attractive to employ a decreased ratio. We reacted varying molar equivalents (8, 4, 3, 2, 1) of dimethylallene with propanal (entry 1) and found that GC yields varied little with 8, 4, and 3 equivalents of the allene. However, when less than three equivalents were used, the yields were lower, consumption of the aldehyde took longer and more by-products were observed. Also noteworthy is that reactions with the aliphatic aldehydes shown in the table proceeded more rapidly than did those with aromatic ketones.[11] Of greater interest and importance for the potential utility of this approach for the synthesis of 2-alkylidene oxetanes was that we noted very little product corresponding to **4** and **5** with these aldehydes.

Perhaps the most striking observation is of the lack of regioselectivity. It is likely that both steric (see Figure) and electronic factors play a role. If the reaction pathway proceeds through a diradical intermediate,[12] the steric congestion for closure of rotamer A is quite severe; thus, steric factors should favor **9**.[13] The importance of steric factors is apparent in the decrease in both yield and regioselectivity with increasing congestion adjacent to the carbonyl moiety. However, the spin density at the disubstituted terminus of the allyl radical should be greater, favoring **8**.[14]



Figure

In order to gain a greater understanding of the role of substituents on the allene in the regiochemical outcome of the Paterno-Büchi reaction, we prepared a range of allenes **10-14**.[15] Allenes **10-13** did not react with isovaleraldehyde, either neat or in solution (pentane, 0.3 M in aldehyde). Nor did they react with aromatic carbonyl compounds. The reason for the lack of reactivity of the monosubstituted alkyl allenes prepared and of the silyl substituted allenes is not immediately apparent, and further investigations are being undertaken on these classes. However, allenol ether **14** reacted with isovaleraldehyde (**15**) with complete regioselectivity to give **16** (80% yield by GC, 40% isolated yield) as a 2:1 mixture of diastereomers.



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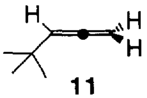

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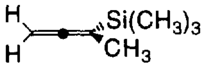

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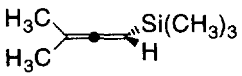

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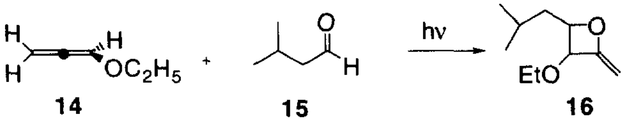

We have demonstrated that the Paterno-Büchi reaction between dimethylallene and alkyl aldehydes can be used to prepare 2-alkylidene oxetanes. Isolated yields are modest, however, and mixtures of regioisomers are produced. Allenol ether **14**, on the other hand, produced a single regioisomer. Use of this moiety may afford a handle for regioselective photocycloadditions, and manipulation of the ether substituent may lead to enhanced stereoselectivity. Predictable regio- and stereoselectivity are crucial if this conceptually attractive approach to 2-alkylidene oxetanes is going to be useful. The results reported here highlight the need for greater understanding of the factors that influence the Paterno-Büchi reaction with allenes. Nevertheless, they also suggest that the investigation may well prove fruitful.

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(9) Alkylidene oxetanes **8** and **9** were isolated as inseparable mixtures in greater than 90% purity. All new compounds gave satisfactory spectroscopic data. The molar ratios of **8** and **9** were determined by both GC and NMR. Compounds **8** and **9** and their molar ratios were readily distinguished by the position of the methylene protons for **8** (d's, J=3.5 Hz at 3.9 and 3.6 ppm) and the C-3 protons for **9** (dd's at 2.6-2.8 and 3.0-3.2 ppm).

(10) The isolation of the 2-alkylidene oxetane mixtures **8/9** proved to be quite problematic. Although distillation was possible, the recoveries were very low (this may be a reflection of scale), and the purity was less satisfactory than with chromatography. Chromatography on flash silica, florisil and neutral alumina destroyed the oxetanes. The results with basic alumina were batch dependent. The most reliable method proved to be to stir flash silica with 0.5-1.0% of triethylamine in the eluting solvent, pack the column and elute with the same solvent mixture. More recently, we have found that basic alumnia deactivated with triethylamine appears to give satisfactory results. However, we have employed these conditions less extensively.

(11) In the earlier reports (see refs. 2 and 3) irradiations were continued for 7-28 days in sealed tubes. We found repeating some of those reactions that, although our yields were similar, the aromatic carbonyl compounds were consumed in 2-4 days, about twice as long as for the aldehydes. This may be an indication that the aldehydes are reacting via a singlet manifold, as singlet reactions are generally more rapid--see ref. 8.

(12) For mechanistic discussions see the appropriate sections of the reviews cited in ref. 8.

(13) For a theoretical treatment of the importance of steric factors in diradical ring closures involving allylic systems see Pasto, D. J.; Sugi, K. D.; Alonso, D. E. *J. Org. Chem.* **1992**, *57*, 1146-1150 and references therein.

(14) Although we were unable to locate calculations of spin densities for dimethyl allyl radicals, such calculations should certainly be possible and will be undertaken. For an approach to such calculations involving unsubstituted allyl radicals see Glaser, R.; Choy, G. S. C. *J. Phys. Chem.* **1993**, *97*, 3188-3198.

(15) Compounds **10** and **11**: Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes: A Laboratory Manual*, Elsevier, New York, 1981, 157. Compound **12**: Danheiser, R. L.; Tsai, Y.-M.; Fink, D. M. *Org. Synth.* **1987**, *66*, 1. Compound **13**: Bennetau, B.; Pillot, J. P.; Dunogues, J.; Calas, R. *J. Chem. Soc., Chem. Commun.* **1981**, 1094. Compound **14**: Rochet, P.; Vatele, J.-M.; Gore, J. *Synthesis* **1994**, 795.

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