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VINYLCYCLOPENTENE SYNTHESIS VIA PHENYLTHIO RADICAL CATALYZED ADDITION OF ELECTRON DEFICIENT ALKYNES TO SUBSTITUTED VINYLCYCLOPROPANES

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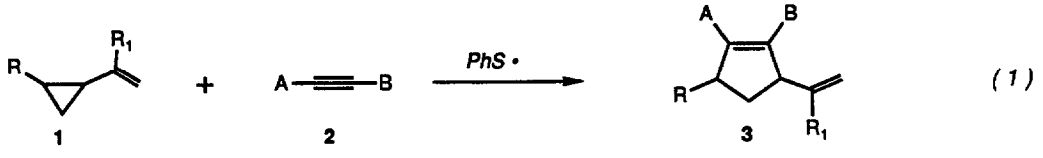
Abstract: Treatment of either t-butyl ester- or benzylether-substituted vinylcyclopropanes with an excess of ester- or sulfone-bearing alkynes in the presence of phenylthio radical in benzene afforded moderate yields of functionalized vinylcyclopentene products as mixtures of stereoisomers.

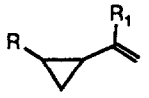
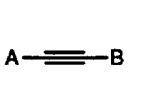
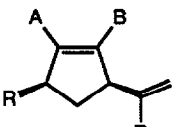
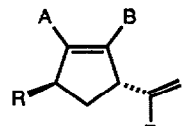
The development of a general free radical mediated [3-atom + 2-atom] strategy for the synthesis of variously substituted five-membered rings has enabled the efficient construction of functionalized 1,2-dioxolane, cyclopentane and tetrahydrofuran species.[1,2] These transformations are catalyzed by an aryl chalcogen radical (ArS• or ArSe•), and utilize either substituted vinylcyclopropane or vinyloxirane substrates as the three atom component in combination with an appropriate two atom addend (alkene, O_2). Extension of this paradigm to include *alkynes* as two atom components would afford a simple route to highly functionalized vinylcyclopentene products (Eq. 1). Herein, we report our preliminary findings describing the scope and potential limitations of this new cyclopentene forming process.



1 2 3 (1)

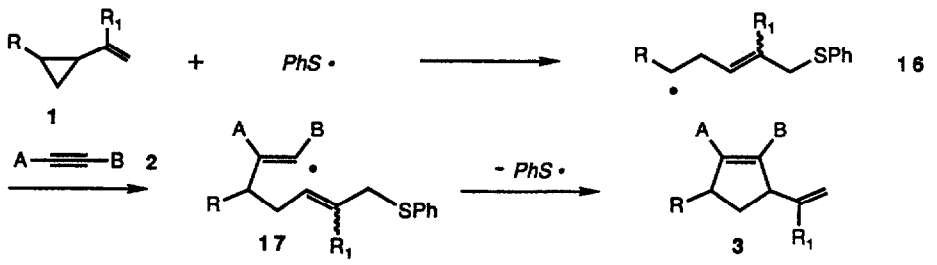
Initial screening reactions were run under standard conditions[3] utilizing the vinylcyclopropanes **4** and **6** in combination with an excess (5-15 eq.) of either methyl propiolate (**7**), the ethynyl sulfone **8**, phenyl acetylene, or ethyl ethynyl ether. Vinylcyclopentene products were formed in the reactions with the electron deficient alkynes **7** and **8**, but not with the latter two species. Optimization of reaction parameters (solvent, temperature, ratio of substrates) led to isolation of the vinylcyclopentene products **10-15** in the yields shown (Table) under the specified conditions (footnote a). Thus, the diester substituted vinylcyclopentenes **10a/10b** result from addition of methyl propiolate (**7**) to the ester substituted vinylcyclopropane **4**, while the analogous sulfone-ester products **11a/11b** arise from reaction with phenyl ethynyl sulfone (**8**). Likewise, *oxygen*-substituted cyclopentenyl esters **13a/13b** and **15a/15b**, or oxygen-substituted cyclopentenyl sulfones **14a/14b**, can be accessed through the benzyl ether of 2-vinylcyclopropanol **6** and the appropriate electron deficient alkyne addend.

In each case, the vinylcyclopentene products were obtained as a mixture of syn-substituted and anti-substituted stereoisomers. Most examples displayed a modest preference for the syn isomer, in accord with expectations.[1] In the analogous vinylcyclopentane series, incorporation of the Lewis acid trimethylaluminum both improved the yield and enhanced stereoselectivity[1a] upon phenylthio radical catalyzed *alkene*/vinylcyclopropane addition. However, in the cyclopentene series, this additive only had a beneficial effect on the combination of vinylcyclopropane **5** with methyl propiolate (**7**) (Table, entry *c* - in refluxing benzene without $AlMe_3$ present, a 39% yield of **12a/12b** (1.4:1 ratio) was obtained). Methyl substitution either on the alkene unit of the cyclopropyl substrate (entry *c*), or on the alkyne moiety (entry *f*) are tolerated, leading to the *propenyl*cyclopentenes **12a/12b** and the tetrasubstituted vinylcyclopentenes **15a/15b**, respectively.

	 R R1		 A B		cond.[a]				yield[d]
a)	**4** CO_2t-Bu	H	**7** H	CO_2Me	A	**10a**	*3.4 : 1*[b]	**10b**	*39 %*
b)	**4** CO_2t-Bu	H	**8** H	SO_2Ph	B	**11a**	*1.9 : 1*[c]	**11b**	*50 %*
c)	**5** CO_2t-Bu	CH_3	**7** H	CO_2Me	C	**12a**	*3.8 : 1*[b]	**12b**	*53 %*
d)	**6** OBn	H	**7** H	CO_2Me	D	**13a**	*1.7 : 1*[b]	**13b**	*50 %*
e)	**6** OBn	H	**8** H	SO_2Ph	E	**14a**	*1 : 1*[c]	**14b**	*36 %*
f)	**6** OBn	H	**9** CH_3	CO_2Me	F	**15a**	*1.5 : 1*[b]	**15b**	*41 %*

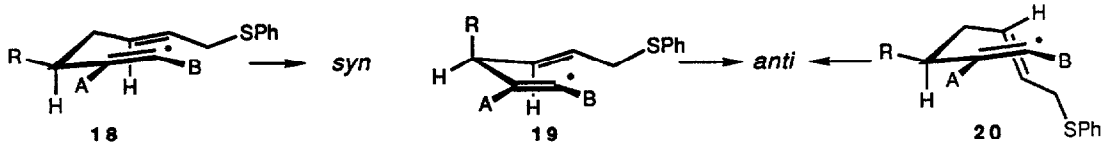
a) A: 15 eq. alkyne, PhH, 23 °C; B: 5 eq. alkyne, PhH, reflux; C: 15 eq. alkyne, 0.8 eq. $AlMe_3$, $PhCH_3$, -30 °C; D: 15 eq. alkyne, PhH, reflux; E: 10 eq. alkyne, PhH, reflux; F: 15 eq. alkyne, PhH, 23 °C. b) Ratio based on GC analysis of the crude reaction mixture. c) Ratio based on ^1H NMR of the crude reaction mixture. d) The vinylcylcopentenes were fully characterized by spectroscopic means (^1H NMR, ^{13}C NMR, IR, MS, HRMS).

By analogy with the mechanism believed to be operational in the related vinylcyclopentane synthesis[1], we suspect that the vinylcyclopentene chemistry transpires as shown in abbreviated form in Eq. 2. The modest yields in the cyclopentene series, in contrast to the yields (50-90%) typically seen in the cyclopentane chemistry, may be a consequence of the diminished reactivity of alkynes relative to alkenes with carbon radicals[4]. In this instance, the homoallylic radical **16** can then engage in undesirable competitive processes, such as polymerization (addition to **1**) or sulfide trapping (addition to Ph_2S_2) to a greater extent than in the alkene addition case.

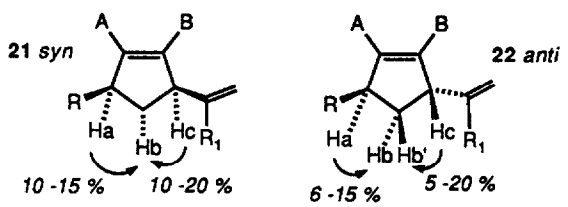


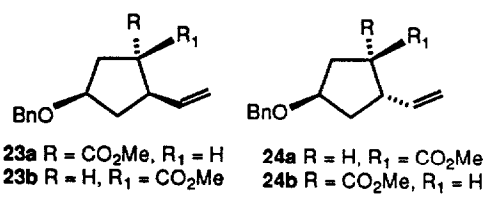
(2)

Product stereochemistry is set during the 5-hexadienyl radical cyclization (**17** → **3**). Cyclization through a chair-like transition state resembling **18** can account for the syn product, while cyclization through either chair **19** or boat **20** transition states can lead to the anti product. The syn preferences seen in the cyclopentene series (ca. 2:1) are substantially lower than those observed with the cyclopentane congeners (ca. 5:1). One factor which may contribute to the erosion of stereoselectivity in the cyclopentene case stems from the slight twist, relative to the cyclopentane series, imparted to the alkenyl radical moiety in **18-20** by the stereoelectronic requirements of bond formation. This "twist" engenders $A^{1,2}$ strain between A and R in the chair-like conformer **18** and thus should diminish its energetic advantage relative to an axial chair conformer **19**. If the boat-like transition state **20** contributes to product formation, it too should suffer a similar energetic penalty.



Product structure and stereochemistry were determined by a combination of spectral techniques and chemical correlation. Thus, syn adducts **21** invariably displayed significant NOE's between Ha and Hb, and Hc and Hb, respectively, while the anti adducts **22** demonstrated similar NOE's between the Ha/Hb pair, and the Hb'/Hc pair of protons. Furthermore, reduction of syn isomer **13a** with Mg/CH_3OH[5] furnished a 77% yield of the vinylcyclopentanes **23a** and **23b** (2.6:1), while similar reduction of the anti isomer **13b** led, in 88% yield, to the vinylcyclopentanes **24a** and **24b** (2.7:1). The complete structure and stereochemistry of the vinylcyclopentanes **23a/b** and **24a/b** have been established earlier in our laboratory[6].





23a R = CO_2Me, R_1 = H
23b R = H, R_1 = CO_2Me

24a R = H, R_1 = CO_2Me
24b R = CO_2Me, R_1 = H

In summary, oxygen- and ester- substituted vinylcyclopentenes **10** - **15** can be prepared by modification of previously developed methodology for vinylcyclopentane synthesis. However, both yield and stereoselectivity in the cyclopentane series are generally lower than observed in the cyclopentane case. The diminished yields and attenuated stereoselectivity can be plausibly traced to subtle mechanistic differences between the free radical chemistry of alkynes and alkenes. Nevertheless, the wealth of functionality on the product cyclopentenes, and the potential for stereoselective conjugate addition to the electron deficient alkene moiety in the product, suggest that these species may find a role in cyclopentanoid natural products synthesis. Efforts in this area are underway, and will be reported in due course.

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3. A typical experiment follows: A deoxygenated solution of Ph_2S_2 (190 mg, 0.86 mmol) and AIBN (27 mg, 0.17 mmol) in 4.0 mL of PhH was added dropwise over 30 h to a room temperature solution of vinylcyclopropane **6** (150 mg, 0.86 mmol) and methyl butynoate (**9**) (1.26 gm, 12.9 mmol) in 6.0 mL of PhH under Ar with concomitant sunlamp irradiation. After addition, the solution was maintained at room temperature until the vinylcyclopropane was consumed (TLC analysis), at which time the solution was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel with 5% Et_2O/hexane as eluent to afford 96 mg of the vinylcyclopentenes **15a** and **15b** (1.5:1) as a colorless oil (41%). Samples of individual stereoisomers could be isolated by additional flash chromatography (silica gel, 5% Et_2O/hexane as eluent) and were completely characterized by spectroscopic means (^1H NMR, ^{13}C NMR, MS, HRMS, IR).
4. Geise, B., Lachein, S. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 768. For example, cyclohexyl radical adds to methyl acrylate three times faster than to methyl propiolate at 20°C. However, subsequent exo cyclization of 5-hexadienyl radicals of the type **17** is quite rapid (~10^8 s^{-1} at 60°C): see Beckwith, A.L.J.; O'Shea, D.M. *Tetrahedron Lett.* **1986**, *27*, 4525.
5. Hudlicky, T.; Sinai-Zingde, G.; Natchus, M.G. *Tetrahedron Lett.* **1987**, *28*, 5287.
6. Unpublished observations. See Ref. 1a, supplemental material for analogous examples.

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