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Intermolecular free radical additions to strained cycloalkenes. Cyclopropene and cyclobutene as radical acceptors

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Abstract

Intermolecular additions of electrophilic radicals to cyclopropene and cyclobutene derivatives afford the addition products in 37–50% yield. The strain relief in the intermediary radical accelerates the addition, as shown by competitive addition experiments. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: radicals and radical reactions; cyclopropenes; cyclobutenes; xanthates; strained compounds.

Intermolecular addition of carbon centered radicals to radicophilic alkenes, known as the radical Michael addition, or Giese addition, is a powerful method for C–C bond formation, whose growing popularity in synthetic organic chemistry is based on high chemo- and regioselectivity, mild reaction conditions, as well as tolerance of a wide range of functional groups.[1] However, due to steric reasons, 1,2-disubstituted alkenes are less efficient radicophilic acceptors (except when both substituents are strongly activating); thus, even the relatively small methyl group in the β-position of the alkene decelerates the rate of addition by two orders of magnitude.[2]

We endeavored to investigate the possibility of using small, highly strained cycloalkenes as acceptor components in free radical additions. It was expected that strain relief in the intermediary radical should provide additional thermodynamic driving force for the reaction, thus increasing the reactivity of this special class of 1,2-disubstituted alkenes.

The reactivity of cyclopropene was tested on a cyclopropenone ketal.[3] Protection of the carbonyl group should eliminate side-reactivity of a highly reactive cyclopropenone. Although **2** is known to undergo the addition of nucleophiles, in terms of electronic matching required for radical addition it can be considered as an electron-rich alkene, calling for an electron-deficient, electrophilic initial radical. Therefore, the reaction was designed as an addition with inverse electron demand, using a xanthate as the radical precursor.[4]

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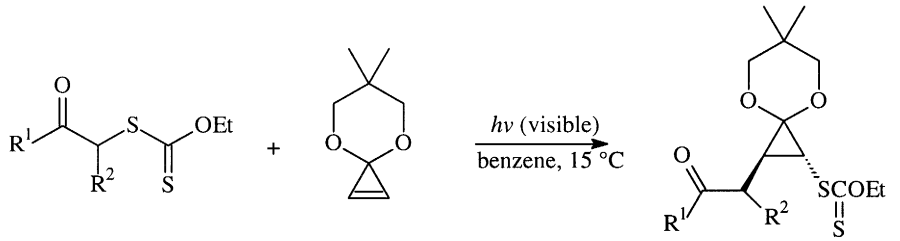
Attempts to effect the addition by heating a solution of **1a** and **2** in benzene, in the presence of dilauroyl peroxide failed, due to the thermally induced dimerization of cyclopropenone ketal **2** (Scheme 1).[3] Low temperature chemical initiation with di-*tert*-butyl peroxydicarbonate or triethylborane was also unsuccessful. However, irradiation of the reaction mixture with UV light afforded the desired adduct **3a**, albeit in low (17%) yield, which is probably a consequence of side reactions induced by UV light. When a benzene solution of **1a** and **2** was irradiated with 250 W Xenofot sunlamp at 15°C, cyclopropanone derivative **3a** was isolated in 46% yield.[5] Xanthate precursors **1b** and **1c** behaved similarly, affording the corresponding adducts in moderate yields. The products **3a–c** were obtained as mixtures of *cis*/*trans* isomers in the ratio of *trans*:*cis*=2.8:1–3.3:1. Surprisingly, structurally more complex xanthate precursors **1d** and **1e** failed to react under the same conditions, indicating that steric hindrance plays an important role with this type of radical acceptor.



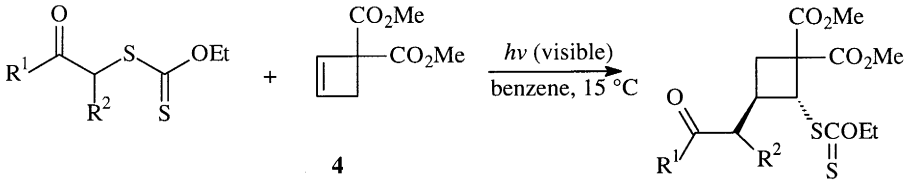
1a R^1=Me, R^2=H
b R^1=OEt, R^2=H
c R^1=OEt, R^2=CO_2Et
d R^1=OEt, R^2=allyl
e R^1=OEt, R^2=Me

2

		trans : *cis*
3a	46%	2.1 : 1
b	37%	3.3 : 1
c	44%	3.3 : 1
d	0%	
e	0%	

Scheme 1.

We then turned our attention toward a next cycloalkene homologue, i.e. cyclobutene.[6] Under the same reaction conditions as above, the reactions of xanthates **1a–c** with 3,3-dimethoxycarbonylcyclobutene **4** proceeded smoothly, affording the corresponding adducts **5a–c** in 40–50% isolated yield (Scheme 2).[5] The additions proceeded with complete regioselectivity, i.e. to the sterically less hindered end of the double bond. The products **5a**, **b** and **c** were obtained as inseparable mixtures of *trans*/*cis* isomers in the ratio of 6/1, 10.4/1 and 8/1, respectively. Unfortunately, methyl substituted xanthate precursor **1e** gave no reaction under these conditions.



1a R^1=Me, R^2=H
b R^1=OEt, R^2=H
c R^1=OEt, R^2=CO_2Et
e R^1=OEt, R^2=Me

4

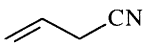
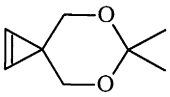
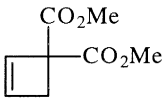
		trans : *cis*
5a	40 %	6 : 1
b	40 %	10.4 : 1
c	52 %	8 : 1
e	0 %	

Scheme 2.

In order to estimate the relative reactivity of cyclopropene and cyclobutene with respect to terminal alkenes and unstrained cycloalkenes, competition experiments with allylcyanide and cyclohexene were performed. The former has been shown to undergo the addition of *t*-butoxycarbonylmethyl radical with

a rate constant of k=3.8×10^4 [M^{-1}s^{-1}] at 23°C.[7] The results of these experiments are summarized in Table 1.

Table 1
Relative rates of addition of **1b** to cycloalkenes and allyl cyanide

Substrate	relative rate	relative rate normalized per number of accepting sp^2 C-atoms
	1	1
	0.95	0.48
	0.29	0.29
	0.26	0.13

The cycloalkenes tested exhibit the expected order of reactivity, which correlates well with the amount of strain built in the acceptor molecule. However, all rate constants fall within the same order of magnitude, indicating that the influence of strain on the reactivity of radicophilic acceptors is limited, in comparison to the electronic and steric effects.

We believe to have shown that small, strained cycloalkenes react with carbon-centered radicals at synthetically useful rates. Apart from offering a potentially useful alternative for the synthesis of cyclopropane and cyclobutane derivatives, the principle of strain-increased reactivity could probably be extended to other strained unsaturated systems, providing an additional thermodynamic driving force for successful C–C bond formation under homopolar conditions.

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5. A typical experimental procedure: In a Pyrex, external water-cooled reactor, a deaerated solution of **1b** (300 mg) and **2** (68.2 mg) in benzene (0.8 ml) was irradiated for 4 h with a 250 W xenophot sun-lamp focalized light, with stirring under an argon atmosphere. After the evaporation of solvent, the product was purified by column chromatography on SiO_2 (eluent benzene:ethyl acetate=95:5), to afford 63.2 mg (37.3%) of **3b** and 240 mg of recovered **1b**. Physical data for **3b**: viscous, light-yellow oil. Anal. calcd for $C_{15}H_{24}O_5S_2$: C 51.70, H 6.94, S 18.40, found: C 51.41, H 6.69, S 18.52; IR_{film}: 2960, 2871,

1737, 1472, 1340, 1289, 1220, 1185, 1136; ^{1}H NMR for *trans*-isomer ($CDCl_3$): 4.66 (q, *J*=7.2, 2H); 4.16 (q, *J*=7.2, 2H); 3.80 (d, *J*=10.8, 1H); 3.39–3.74 (m, 3H); 2.66 (d, *J*=6.8, 1H); 2.62 (d, *J*=7.4, 1H); 2.40 (d, *J*=6.0, 1H); 1.68–1.79 (m, 1H); 1.40 (t, *J*=7.2, 3H); 1.27 (t, *J*=7, 3H); 1.14 (s, 3H); 0.86 (s, 3H); ^{13}C NMR for *trans*-isomer ($CDCl_3$): 215.33 (C); 171.62 (C); 90.37 (C); 76.00 (CH_2); 75.87 (CH_2); 69.86 (CH_2); 60.63 (CH_2); 32.14 (CH); 32.10 (CH_2); 30.72 (C); 27.76 (CH); 22.46 (CH_3); 21.97 (CH_3); 14.11 (CH_3); 13.73 (CH_3); $MS/CI_{isobutane}$: 349 (M+1), 227 (M–121). Physical data for **5c**: viscous, light-yellow oil. Anal. calcd for $C_{18}H_{26}O_9S_2$: C 47.99, H 5.82, S 14.23; found: C 47.71, H 5.73, S 14.31; IR_{film}: 2983, 2956, 1906, 1735, 1370, 1277, 1163, 1115, 1096; ^{1}H NMR for *trans*-isomer ($CDCl_3$): 5.10 (d, *J*=9.8, 1H); 4.63 (q, *J*=7.3, 2H); 4.21 (q, *J*=7.1, 4H); 3.79 (s, 3H); 3.76 (s, 3H); 3.56 (d, *J*=8.7, 1H); 3.18 (m, 1H); 2.85 (dd, J_1=12.0, J_2=9.5, 1H); 2.36 (dd, J_1=12.0, J_2=9.3, 1H); 1.41 (t, *J*=7.1, 3H); 1.27 (t, *J*=7.1, 3H); 1.25 (t, *J*=7.1, 3H); ^{13}C NMR for *trans*-isomer ($CDCl_3$): 211.91 (C); 169.82 (C); 169.22 (C); 167.16 (C); 70.21 (CH_2); 61.63 ($2\times CH_2$, superimposed); 56.12 (C); 55.04 (CH); 52.75 (CH_3); 52.69 (CH_3); 49.16 (CH); 36.60 (CH); 30.88 (CH_2); 13.90 (CH_3); 13.86 (CH_3); 13.46 (CH_3); $MS/CI_{isobutane}$: 451 (M+1).

6. For an intermolecular radical addition to strongly activated cyclobutene derivative, see: Campbell, E. F.; Park, A. K.; Kinney, W. A.; Fengl, R. W.; Liebeskind, L. S. *J. Org. Chem.* **1995**, *60*, 1470–1472.
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