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ACCELERATION OF THE 4-*EXO* RADICAL CYCLIZATION TO A SYNTHETICALLY USEFUL RATE. CYCLIZATION OF THE 2,2-DIMETHYL-5-CYANO-4-PENTENYL RADICAL

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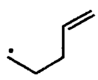
Abstract: The title radical, formed in the reaction of the corresponding bromide with Bu_3SnH, cyclizes in a 4-*exo* fashion to give the (3,3-dimethylcyclobutyl)cyanomethyl radical. At 50 °C, the rate constant for cyclization is $1.9 \times 10^4\ s^{-1}$.

Applications of radical methodology for the production of carbocycles in the syntheses of complex molecules have evolved at an explosive rate during the past several years.[2] By far, the most frequent applications have involved formation of five-membered rings by 5-*exo* cyclizations of 5-hexenyl radicals, but larger rings, including macrocycles,[3] also can be produced by radical cyclizations. For small rings, *exo* cyclizations of the 3-butenyl and 4-pentenyl radicals are endergonic. The rate constant for 3-*exo* cyclization of the 3-butenyl radical is ca. 8000 s^{-1} at 25 °C,[4] and the rate constant for ring opening of the cyclopropylcarbinyl radical is $1 \times 10^8\ s^{-1}$ at 25 °C.[6] Thus, the ring formation is unfavored by about 5.6 kcal/mol, and 3-*exo* cyclizations commonly are followed by fragmentations that can result in 1,2-group transfers.[2a,7] The rate constant for the 4-*exo* cyclization of the 4-pentenyl radical (**1**) to the cyclobutylcarbinyl radical (**2**), while not measured, is certainly very small, and reports of four-membered ring formations by 4-*exo* radical cyclizations are rare.[8] The rate constant for ring opening of radical **2** is estimated to be $1 \times 10^4\ s^{-1}$ at 60 °C,[9] and the rate constant for cyclization of **1** at this temperature should lie between 0.1 and 1 s^{-1} given that the strain energy in the cyclobutyl and cyclopropyl rings are comparable. Herein we report the first measured rate constant for a 4-*exo* radical cyclization, rearrangement of the title radical (**3**) to the cyclobutylcarbinyl radical **4**. The results suggest that appropriately substituted 4-pentenyl radicals can be useful intermediates in the synthesis of cyclobutane products or for 1,3-group transfers by addition-fragmentation sequences.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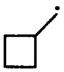
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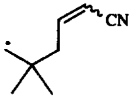

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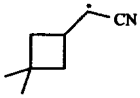

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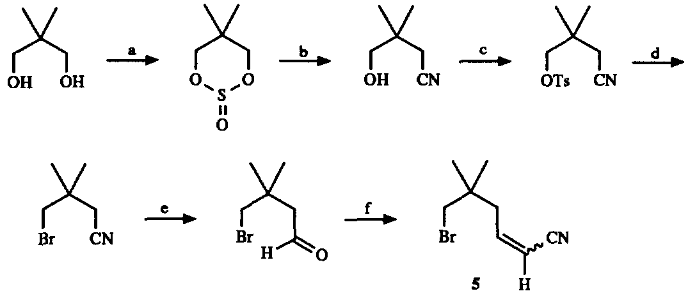
For practical synthetic applications, the pseudo first order rate constant for a radical reaction at 25 °C should exceed 1000 s^{-1}.[2b] Based on kinetic considerations discussed below, we anticipated that steric effects resulting from the addition of *gem*-dialkyl groups onto the 4-pentenyl chain and an electronic effect from the addition of a cyano group onto the olefin terminus would result in a reasonably fast cyclization of radical **3** even if the rate constant for the cyclization of the unsubstituted parent is only 0.1 s^{-1} at 60 °C. The precursor for radical **3**, bromide **5**, was prepared by the sequence shown in Scheme 1. Authentic samples of the acyclic (**6**) and cyclic (**7**) products that result from tin hydride reduction of bromide **5** also were prepared.[10]

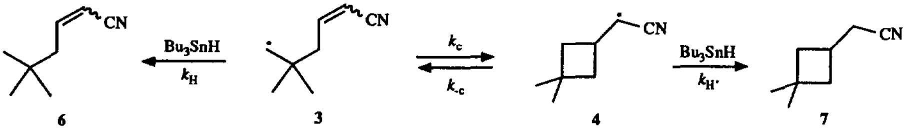
Scheme 1



Conditions: (a) 2.5 equiv $SOCl_2$ in ether, 0 °C, 2 h, 90-93%. (b) 3 equiv NaCN in DMSO, 120 °C, 5 h, 66%. (c) 2 equiv TsCl in pyridine, 0 °C, 12 h, 70% crude. (d) 3 equiv LiBr in DMSO, 120 °C, 3 h, 93% crude. (e) 1 equiv DIBAH in CH_2Cl_2, 20 °C, 0.3 h, 73% crude. (f) 1.1 equiv $(EtO)_2P(=O)CH(Li)CN$ in THF, 60 °C, 0.5 h, silica gel chromatography (hexanes/EtOAc), 23%, E:Z = 2:1.

Scheme 2 shows the reactions of interest for a kinetic analysis. In the tin hydride reductions, radical **3** can be reduced in a second order reaction with rate constant k_H or can cyclize in a unimolecular process with rate constant k_c to give the cyclobutylcarbinyl radical **4**. Cyclic radical **4** also can be reduced in a second order reaction (rate constant $k_{H'}$) or ring open to give **3** (rate constant k_{-c}). The velocity of formation of acyclic product **6** is given by eq 1, and the velocity of formation of cyclobutane **7** is given by eq 2 where a steady state approximation has been applied for radical **4**. At constant concentrations of tin hydride, the ratio of **6** to **7** is given by eq 3.

Scheme 2



$$d[6]/dt = k_H\,[3]\,[Bu_3SnH] \tag{1}$$
$$d[7]/dt = k_{H'}k_c[3][Bu_3SnH](k_{-c} + k_{H'}[Bu_3SnH])^{-1} \tag{2}$$
$$[6]/[7] = k_H k_{-c}/k_{H'}k_c + k_H[Bu_3SnH]/k_c \tag{3}$$

Bromide **5** was allowed to react in the presence of Bu_3SnH at 50 °C using two protocols. In method A, reactions were conducted in benzene with excess Bu_3SnH. Lower concentrations of Bu_3SnH were achieved with catalytic Bu_3SnCl and excess $NaBH_3CN$ in THF (method B).[11] Reactions were initiated by decomposition of AIBN; due to the low concentrations of reagents employed, the radical chain lengths were short, and relatively large amounts of the initiator were used (10 mole-% for method A and up to 50 mole-% for method B). The Table contains some of the results. For the reactions run by method A, the concentration of Bu_3SnH given is the average concentration based on the observed conversion of **5**. For reactions run by method B, the reduction of Bu_3SnX by $NaBH_3CN$ was assumed to be fast, and the concentration of Bu_3SnH given is the initial concentration of Bu_3SnCl. When the reactions containing higher concentrations of tin hydride were allowed to proceed for extended periods (data not included), slight increases in the ratio of cyclobutane **7** to acyclic product **6** were observed apparently due to slow destruction of the acyclic α,β-unsaturated nitrile **6**.

Table. Yields of Products from Reactions of Bromide 5 at 50 °C[a]

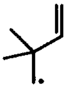
Method	$[Bu_3SnH]$, M	time, h	%5	%6	%7
A[b]	0.046	3	14	59	5
A	0.036	6.5	18	51	6
A	0.018	4	43	29	7
A	0.009	3	70	13	5
A	0.008	22	49	16	8
B[c]	0.003	6.5	4	36	37
B	0.003	8	3	43	45
B	0.002	23	8	14	25
B	0.0018	10	53	12	12
B	0.0018	16	30	19	20

[a]Absolute yields determined by GC against an internal standard. [b]Benzene solvent, 0.01 M **5**, excess Bu_3SnH. [c]THF solvent, 0.01 M **5**, catalytic Bu_3SnCl, excess $NaBH_3CN$.

A plot of **6**/**7** versus $[Bu_3SnH]$ for all of the data in the Table has a slope of (241 ± 7) M^{-1} and an intercept of (0.26 ± 0.13) (errors are 1σ). At the low concentrations of Bu_3SnH in THF, it is possible that hydrogen atom abstraction from the solvent was a major reaction for radical **3** in the method B studies,[12] but the data for only the method A reactions has a slope of (247 ± 12) M^{-1} and an intercept of (0.05 ± 0.3). At 50 °C, the rate constant for reaction of Bu_3SnH with a neopentyl type radical is 4.7 x 10^6 M^{-1} s^{-1}.[5] This value for k_H and the slope in eq 3 give a value for the rate constant k_c at 50 °C of 1.9 x 10^4 s^{-1}.

The cyclization of radical **3** is fast enough to be synthetically useful by Giese's criterion.[2b] However, in our studies, the rapid trapping of **3** by Bu_3SnH limited the yield of cyclic product **7**. Attempts to conduct radical chain reductions of bromide **5** with the poorer hydrogen atom donor Ph_3SiH[13a] with both AIBN and $(PhCO_2)_2$ initiation were not successful. One might anticipate, however, that a decarboxylative route to radical **3** (for example, from a Barton PTOC ester[13]) could be used successfully with a silane or other poor hydrogen atom donor.

It is common to assume that kinetic data for carbon radical reactions can be transferred from one system to another without the introduction of substantial errors. The *gem*-dimethyl substituted 3-butenyl radical **8** cyclizes to **9** 333 times as fast as its unsubstituted parent at 50 °C due to a Thorpe-Ingold effect.[14,15] When a cyano group was added to the terminus of the 5-hexenyl system (radical **10**), the cyclization to **11** at 50 °C was accelerated 275-fold over that of the parent, 5-hexenyl.[17] If one expects the two effects to be additive in radical **3**, a 90,000-fold rate acceleration for cyclization is predicted; assuming a rate constant of 0.1 to 1 s^{-1} for cyclization of the simple 4-pentenyl radical **1** at 50 °C, the predicted rate constant for cyclization of **3** is 1-10 x 10^4 s^{-1}. Therefore, it appears that one can successfully use kinetic data from some 3-*exo* and 5-*exo* cyclizations to predict effects in 4-*exo* cyclizations; a rate constant of 0.2 s^{-1} for cyclization of **1** at 50 °C is the recommended starting value. By this reasoning, the *gem*-dimethyl effect alone should accelerate the cyclization of the 4-pentenyl radical to ca. 70 s^{-1} at 50 °C which is consistent with Beckwith's observation that 2,2-dimethyl- and 3,3-dimethyl-4-pentenyl radicals did not cyclize in the presence of dilute Bu_3SnH.[16]



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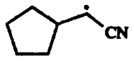

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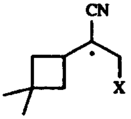
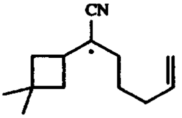


12: X = $SnBu_3$ or SPh



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Our data provide a limit for the rate constant for opening of radical **4**. The intercept of eq 3 is less than 0.5, and dividing this value by the slope gives a limit for k_{-c}/k_{H} of 0.002 M. Rate constants for reactions of stabilized radicals like **4** with Bu_3SnH are not available, but they are typically assumed to be similar to those for reactions of simple alkyl radicals. If the rate constant for trapping **4** by Bu_3SnH at 50 °C is $1 \times 10^6\ M^{-1}\ s^{-1}$, then the rate constant for ring opening of **4** is $< 2000\ s^{-1}$. This limit is small enough such that good yields of cyclobutane products would be expected if a 4-*exo* radical cyclization produced a species capable of a fast follow-up intramolecular reaction such as a fragmentation[18a,b] (as in **12**) or a second cyclization (as in **13**).

We conclude that cyclobutane formations or 1,3-group transfers can be accomplished by radical routes when the precursor 4-pentenyl radical contains both the steric and electronic accelerating factors present in radical **3** and when fast radical trapping agents like Bu_3SnH are avoided. The substitution of carboalkoxy for cyano in **3** would be expected to have a minor effect on the rate constant for cyclization based on the similar rate constants for radical additions to acrylonitrile and methyl acrylate,[18c,d] and it is possible that one could employ vicinal *cis* substitution on a ring for a steric effect. Whether or not radical methodology is incorporated into synthetic schemes for cyclobutane formation and 1,3-group transfer remains to be seen; the constraints for a radical approach are severe, but other methods to effect such transformations are limited.

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10. Compound **6** was prepared from 3,3-dimethyl-1-butanol by oxidation with CrO_3 and reaction of the product aldehyde with $(EtO)_2P(=O)CH(Na)CN$; the product was a 1.9:1 *E*:*Z* mixture. Compound **7** was prepared from 2,2-dimethyl-1,3-propandiol by reaction with TsCl, reaction with NaI, reaction with ethyl malonate and KOH, saponification, pyrolysis at 180 °C, $LiAlH_4$ reduction, reaction with TsCl, and displacement with NaCN. Compounds **6** and **7** from reactions of bromide **5** were identical to the authentic samples by GC and mass spectrometry.
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