Rate Constants for 5- and 6-Exo Secondary Alkyl Radical Cyclizations onto *N,N*-Diphenylhydrazones

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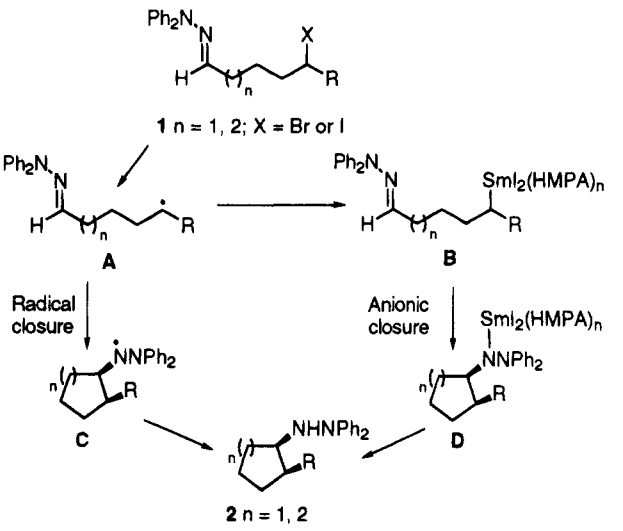
Summary: Competitive "radical clock"-type cyclizations of hydrazones and alkenes established that the rate constants for 5-exo cyclizations onto *N,N*-diphenylhydrazones are 1.1×10^8 s^{-1} and 4.6×10^7 s^{-1} at 80 °C to the *cis*- and *trans*-cyclopentylhydrazines, respectively (about 200 times faster than the corresponding cyclization rate for 5-exo alkenes). The 6-exo hydrazone rate constant is 9.4×10^5 s^{-1} at 80 °C for both cis and trans isomers with activation barriers of 5.6 and 6.2 kcal/mol, respectively.

The interest in free radical reactions applied to synthetic problems continues to advance, and these reactions have been used successfully for a growing number of synthetic targets.[1] These synthetic applications and related mechanistic studies depend on a knowledge of the rate constants for the various radical reactions both to establish the presence of radical intermediates and to control the radical kinetics and hence the product distribution.[2] We have recently reported our initial results of an aza-Barbier reaction in which halohydrazones are cyclized directly under either *n*-Bu_3SnH- or SmI_2/HMPA-mediated conditions to afford hydrazines (**1** to **2**, Scheme 1).[3] The related reaction with carbonylhydrazones provided access to β-amino alcohols after hydrazine reduction with a high level of diastereoselectivity. In contrast to the extensive literature containing kinetic information on free-radical additions onto carbon–carbon double bonds, there are limited kinetic data for carbonyl and imine bonds.[4] The following experiments have been conducted to establish whether the samarium diiodide reactions proceeded by a radical or anionic mechanism, to obtain rate constants for 5- and 6-exo hydrazone ring closures, and to utilize this information to ascertain the synthetic potential for employing the nitrogen-centered intermediate in tandem processes. These studies provide strong evidence for the radical nature of the samarium reactions and established that the rate constant for the 5-exo hydrazone ring closure to the cis isomer is 1.1×10^8 s^{-1} at 80 °C (approximately 200 times faster than the corresponding 5-exo alkene cyclization).

Scheme 1. SmI_2/HMPA Mediated Cyclization onto Hydrazones



The two possible mechanistic pathways for the SmI_2-induced cyclizations are illustrated in Scheme 1. These involve a single electron transfer to generate the carbon radical **A** followed by cyclization to the hydrazine radical **C** and quenching to give **2**, or alternatively, a second electron transfer step may occur at the carbon radical to form the organosamarium intermediate **B** with subsequent anionic cyclization to **D**. For the tin hydride mediated reactions only the radical pathway will be followed. To distinguish between these possibilities, the bromides **3** and **4**, which contain an internal "radical clock",[2,5] were synthesized (Scheme 2). Treatment of **3** in refluxing benzene with *n*-Bu_3SnH and azobis(isobutyronitrile) (AIBN) (Table 1, entry a) allowed a direct measure of the competitive *radical*-based 5-exo cyclization onto alkene versus hydrazone. On the basis of ^1H NMR analysis of the total product mixture, hydrazine **5** was the exclusive product (84% isolated yield) and none of the alkene product **7** was detected. Clearly this radical cyclization onto the imine bond was considerably faster than onto the alkene, with a lower limit for the rate constant of 1.9×10^7 s^{-1} at 80 °C.

Our previous[3] synthetic studies revealed that better stereochemical control of the halohydrazone cyclizations was achieved at low temperatures through the use of SmI_2/HMPA. Recently Hasegawa and Curran[6] reported that the yield of radical product(s) in SmI_2 reactions varied with HMPA concentration. They established that with 2–3 equiv of HMPA/SmI_2 the rate constant for the reduction of a primary carbon radical was $\sim 1 \times 10^6$ M^{-1} s^{-1} at 25 °C. Our standard conditions [SmI_2 (4.0 equiv), THF (40 mL), HMPA (2.0 mL) per mmol of substrate]

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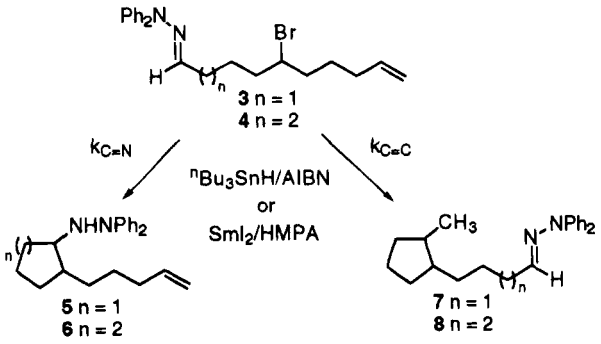
Table 1. Rate Data for Cyclization of Halohydrazones

entry	compd	T (°C)	reagent	ratio (cis/trans)	$k_{C=N}^{cis}$	$k_{C=N}^{trans}$
a	**3**	80	$^nBu_3SnH$, AIBN	**5/7** >25:1[a]	$>1.9 \times 10^7$	$>1.9 \times 10^7$
b	**3**	21	SmI_2, HMPA[b]	**5/7** >25:1	$>2.8 \times 10^6$	$>2.8 \times 10^6$
c	**3**	−42	SmI_2, HMPA	**5/7** >25:1	$>1.3 \times 10^5$	$>1.3 \times 10^5$
d	**4**	80	$^nBu_3SnH$, AIBN	**6/8** 2.5:1 (1:1)	9.4×10^5	9.4×10^5
e	**4**	21	SmI_2, HMPA	**6/8** 2.9:1 (1.3:1)	1.8×10^5	1.4×10^5
f	**4**	−10	SmI_2, HMPA	**6/8** 3.5:1 (1.4:1)	5.9×10^4	4.3×10^4
g	**4**	−42	SmI_2, HMPA	**6/8** 4.5:1 (1.6:1)	1.4×10^4	8.6×10^3

[a] These ratios represent lower limits based on ^1H NMR analysis of the total product mixture. [b] SmI_2 (4.0 equiv), THF (40 mL), and HMPA (2.0 mL) per 1 mmol of substrate. Range of isolated yields 75–93%.

Scheme 2. Competitive Hydrazone–Alkene Radical Cyclizations



and the dropwise addition of SmI_2 ensured a lower concentration of SmI_2 than required for the formation of an organosamarium intermediate considering the fast radical ring closure estimated from the Bu_3SnH experiment described above.[7] Treatment of **3** under these conditions at 21 °C (Table 1, entry b) was also highly chemoselective and afforded only the cyclic hydrazine **5**. A similar result was obtained at −42 °C (entry c).

The 5-hexenyl "radical clock" is thus too slow to determine the 5-exo hydrazone closure rate, but examination of the homolog **4** permitted the measurement of the rate constant for the 6-exo hydrazone cyclization. Under tin hydride conditions, the intermediate radical may partition itself between the 5-exo alkene and 6-exo hydrazone pathways. At 80 °C (entry d) a mixture of products resulted in which the hydrazine **6** predominated (2.5:1) as a 1:1 cis/trans mixture (Scheme 2). The calculated value for the 6-exo hydrazone rate constant for the cis and trans cyclization of a secondary radical is therefore 9.4×10^5 s^{-1}.

The results with SmI_2/HMPA and substrate **4** at various temperatures (Table 1, entries e–g) indicated that both the cis/trans selectivity and the chemoselectivity increased with decreasing temperature. Thus, at −42 °C the 6-exo hydrazone cyclization was 4.5 times faster than the 5-exo alkene ring closure. The 6-exo activation energies were calculated from a plot of the ln of these cis and trans rate constants versus $1/T$ (Figure 1).[8] These values are 5.6 and 6.2 kcal/mol for the cis and trans isomers, respectively, compared to the values of 6.5 and 7.4 kcal/mol[9] for the corresponding cis and trans 5-exo alkene cyclizations.

The 5-exo rate constant was determined from the tin hydride mediated reaction of bromide **9** to form either

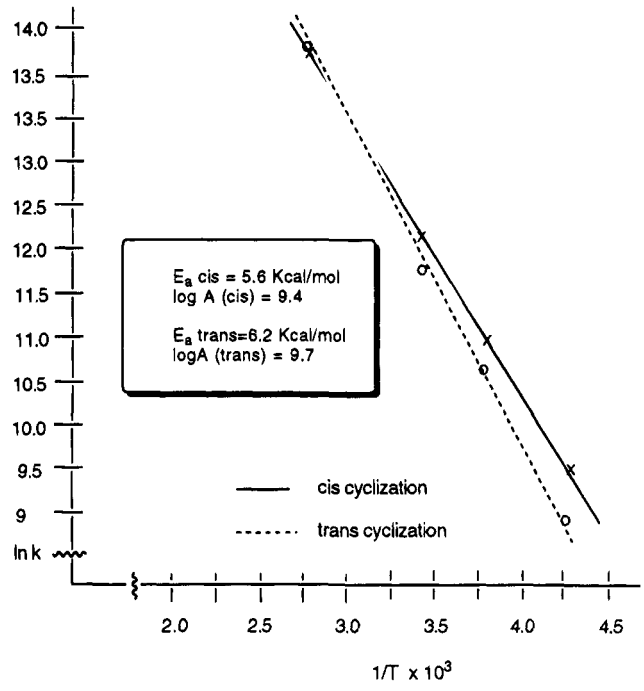
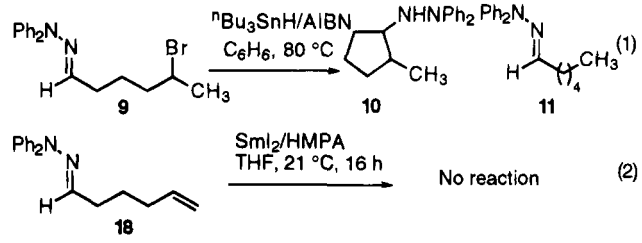


Figure 1. Determination of activation energies for cis and trans 6-exo hydrazone cyclizations.



the cyclic hydrazine **10** or the reduced hydrazone **11** (eq 1) based on the known rate constant for the quenching of a secondary radical with n-Bu_3SnH (3×10^6 M^{-1} s^{-1} at 80 °C).[5] Treatment of **9** with n-Bu_3SnH (2.4 M, 2.0 mL in 1.0 mL benzene plus AIBN, 80 °C) afforded both the cyclized hydrazine **10** and the reduced product **11** (18.2:1 as a 2.5:1 cis/trans mixture, 91% isolated yield). Thus, the secondary radical rate constants for the cis and trans 5-exo hydrazone cyclizations are approximately 1.1×10^8 s^{-1} and 4.6×10^7 s^{-1}, respectively. These values are tabulated in Scheme 3 with some related carbocyclic examples for comparison.

Ketones **12** and **13** were also investigated to establish the reactivity profile of the samarium ketyl radicals (Scheme 4).[10] At 21 °C with SmI_2/HMPA ketone **12** cyclized exclusively to the hydrazine-alcohol **14** as a

(7) TLC analysis of the reaction indicated that the samarium diiodide was being consumed as the drops were added although the SmI_2:HMPA ratio varied with time.

(8) Data and temperatures from Table 1 afforded log A values of 9.4 and 9.7 for the respective cis and trans cyclizations (fit $r = 0.999$ for both plots).

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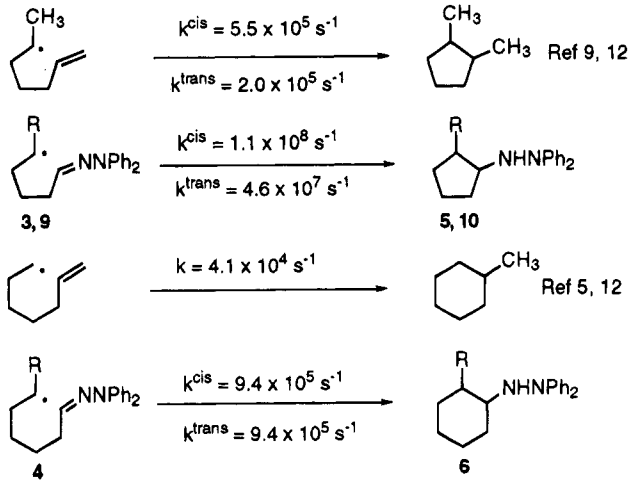
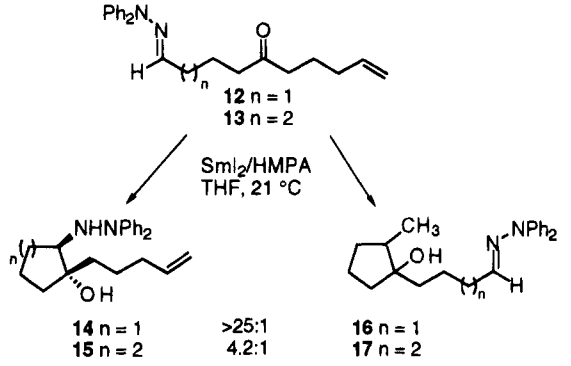
(10) For examples of samarium diiodide promoted cyclization of olefinic ketones see: Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132.

Scheme 3. Rate Constants for 5- and 6-Exo Cyclizations at 80 °C



Scheme 4. Competitive Carbonylhydrazone–Carbonylalkene Cyclizations



single diastereomer in 72% isolated yield with the hydrazine and hydroxy group *trans*. The reactivity pattern of **13** with SmI_2/HMPA was similar to **4** and generated both possible cyclic alcohols **15** and **17** from 6-exo hydrazone and 5-exo alkene cyclization, respectively (4.2:1). To be certain that electron addition to the imine double bond was not a competing pathway, the unsaturated hydrazone **18** was examined and was shown to be inert under our standard conditions.

In conclusion, the 5-exo hydrazone radical cyclizations have been shown to be a fast reactions, proceeding approximately 200 times faster than the corresponding 5-exo alkene ring closures. The 6-exo hydrazone cyclization has also been demonstrated to be faster than the 5-hexenyl cyclization. Similarly, in view of the numerous radical cyclizations onto oxime ethers,[11] and their similar characteristics, it seems likely they will also undergo ring closure more rapidly than simple alkenes. The hydrazone kinetic data, coupled with the efficiency and high diastereoselectivity of the examples described above, will allow the rational design of various tandem cyclizations for the total synthesis of natural products. The application of these results to specific targets will be reported in due course.

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Supplementary Material Available: Rate constant calculations and experimental procedures for the preparation of compounds **3-6**, **8**, **10-15**, **17**, and **18** including spectral data (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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