Samarium(II) Iodide Induced Radical Cyclizations of Halo- and Carbonylhydrazones

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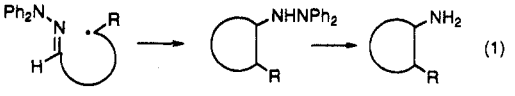
Intramolecular radical cyclizations have received considerable attention in recent years.[1] Similarly, synthetic applications of SmI_2 include a variety of coupling and cyclization reactions.[2] A liability inherent in classical radical precursors is the net loss of the two participating functional groups. This severely limits, at an early stage in a synthetic sequence, the use of conventional radical cyclizations. One solution employs α-heteroatom radical intermediates in the cyclization step to generate products that retain synthetically useful functionality for subsequent manipulation.[3] Previously we have used oxathiolanes and oxathiolanones for this purpose to generate cycloalkanols.[4] An alternative approach is to trap the cyclic radical with unsaturated functional groups, but this is often disappointing.[5] However, with a heteroatom in the addition terminus, the efficiency should improve, and useful functionality will be incorporated into the product as illustrated (eq 1). We wish to report the first examples in which



(1)

R = H, OH, Me, ^{i}Pr, Cy

halo- and carbonylhydrazones are cyclized directly under either ^{n}Bu$_3$SnH or SmI_2 mediated conditions to afford hydrazines. This intramolecular cyclization is the synthetic equivalent of an aza-Barbier reaction. These reactions display a high level of diastereoselectivity and, with aldehydes and ketones, provide rapid access to β-amino alcohols after hydrazine reduction.

Oxime ethers have been utilized previously with ketyl, alkyl, and vinyl radicals[6] and for reductive coupling of carbonyl compounds.[7] In special circumstances, alkyl radicals cyclize onto aldehyde carbonyls in preference to alkenes.[8] Aryl radicals add to aldimines,[9] but hydrazones have received much less attention. The previous example[10] involved cyclization onto *N*-aziridinyl imines followed by fragmentation and N_2 loss to yield carbocycles. Thus it was not clear, at the outset, if this feature was essential for successful cyclization of hydrazones. In principle, with standard hydrazones, the nitrogen radical intermediate could also be used to conduct further chemistry, and hydrazine cleavage would yield amines.

To ascertain the synthetic potential of *N,N*-diphenylhydrazones as radical acceptors and the level of diastereoselectivity that could be anticipated, the required substrates were prepared from the appropriate lactones.[11] Reduction yielded lactols which condensed with *N,N*-diphenylhydrazine to provide the (*E*)-hydrazones exclusively.[12] Selective oxidation of the resulting alcohol was accomplished with sulfur trioxide–pyridine,[13] as pyridinium chlorochromate failed and Swern oxidation was unreliable. Chemoselective addition of the appropriate Grignard reagent afforded the secondary alcohols,[14] which were converted to the halides with triphenylphosphine and Br_2 or I_2.[15]

Table 1 summarizes the results with several 5-halopentyl-*N,N*-diphenylhydrazones. Initially, bromide **1** was treated with tributyltin hydride and azobis(isobutyronitrile) (AIBN) in refluxing benzene (Table 1, entry a). The reaction proceeded smoothly to give excellent yields (95%) of the cyclopentylhydrazine, although with modest *cis/trans* selectivity. Samarium diiodide (4.5 equiv) in THF/HMPA [40 mL/1.5 mL (~2.5 equiv)/1 mmol of halide] at room temperature (21 °C) yielded similar results (Table 1, entry b). A significant improvement in diastereoselectivity (7:1; 11:1) was achieved at lower temperatures (–42 °C, X = Br; –78 °C, X = I) (Table 1, entries d, e) and as the bulk of the substituent increased (Table 1, entries f–h). In contrast to iodide **2**, bromide **1** was unreactive at –78 °C with SmI_2. Also, with large alkyl substituents (Table 1, entries f–h), the bromides **3** and **4** were inert to SmI_2 at –42 °C but reacted readily at –10 °C. In all cases, the *cis*-substituted cyclopentane was the preferred isomer. Similar results were achieved for the cyclohexane systems listed in Table 2, although the selectivities were lower.[16] The tin hydride examples (Table 2, entries a and f) established the efficiency of these cyclizations and provided a useful comparison with SmI_2. Additional "radical clock" studies have confirmed the radical nature of the SmI_2 reactions.[17]

In contrast to the temperature trends in the halide examples, reductive cyclizations of the carbonyl systems **10–13** were more

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(3) The use of SmI_2 allows a second electron transfer to generate reactive organosamarium species for nucleophilic reactions.[2c]

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(11) Synthetic details in the supplementary material.

(12) This stereochemical result is in contrast to the syn/anti mixture that usually results from the preparation of oxime ethers. (a) Brady, O. L.; Bishop, G. *J. Chem. Soc.* **1925**, *127*, 1357. (b) Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3.

(13) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(14) In THF at 0 °C, there was no evidence for addition to the imine bond encountered with some hydrazones. The exception was the addition of ^{i}PrMgCl to aldehyde **5**; at 0 °C, the ratio was 10:1, but the selectivity increased to >25:1 at –78 °C. (a) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224. (b) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 4563.

(15) In the sterically more hindered alcohols, the halides were accompanied by elimination products, and only the bromides could be prepared.

(16) The relative stereochemistry was established by comparison with authentic samples prepared from the corresponding cycloalkanones and NOE experiments. Diastereomers were readily separated by silica gel chromatography, and, as has been observed previously, the higher field methine ^{13}C NMR resonance was associated with the *cis* isomer.[4,6c] Ley, G. C.; Lichter, R. L.; Nelson, A. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, 2nd ed.; J. Wiley and Sons: New York, 1980.

(17) The reducing power of SmI_2 is minimized at low concentrations and with less than 5 equiv of HMPA. Thus it was established (Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717) that the maximum yield of radical product(s) was produced with 2–3 equiv of HMPA/SmI_2 with a bimolecular rate constant of $\sim 1 \times 10^6$ M^{-1} s^{-1} for the second electron transfer. Our standard conditions and the dropwise addition of the SmI_2 ensured a lower concentration than normally required for efficient formation of an organosamarium intermediate. Under these conditions, cyclization of 5-hexenyl systems was not competetive with cyclization of 5-hexenylhydrazones. In addition, our related studies have established that intramolecular 5-exo cyclization onto an *N,N*-diphenylhydrazone was >100 times faster than the corresponding 5-exo cyclization onto an alkene (Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.*, submitted for publication).

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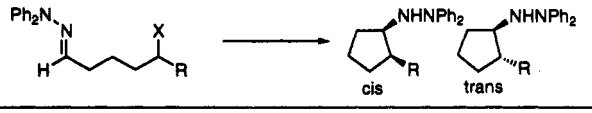
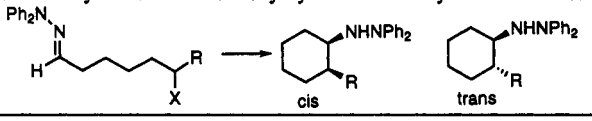
Table 1. Cyclization of Halohydrazones to Cyclopentylhydrazines



entry	substrate	X	R	t, °C	reagent	yield,[a] %	ratio *cis*/*trans*[b]
a	**1**	Br	Me	80	^{n}Bu$_3$SnH	95	2:1
b	**1**	Br	Me	21	SmI_2	91	2:1
c	**1**	Br	Me	0	SmI_2	85	3:1
d	**1**	Br	Me	–42	SmI_2	88	7:1
e	**2**	I	Me	–78	SmI_2	62	11:1
f	**3**	Br	^{i}Pr	–10	SmI_2	70	10:1
g	**4**	Br	Cy	21	SmI_2	89	6:1
h	**4**	Br	Cy	–10	SmI_2	67	9.4:1

[a] Yields are for isolated chromatographically homogeneous material. [b] Ratios were determined from ^{1}H NMR analysis of total product mixture. [c] SmI_2 (4.5 equiv), THF (40 mL), and HMPA (1.5 mL) per 1 mmol of substrate.

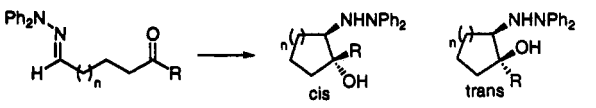
Table 2. Cyclization of Carbonylhydrazones to Hydrazino Alcohols



entry	substrate	n	R	t, °C	reagent[c]	yield,[a] %	ratio *cis*/*trans*[b]
a	**5**	Br	H	80	^{n}Bu$_3$SnH	92	
b	**5**	Br	H	21	SmI_2[c]	85	
c	**6**	Br	Me	–42	SmI_2	63	3:1
d	**7**	I	Me	–78	SmI_2	75	5:1
e	**8**	I	Cy	–78	SmI_2	75	1.3:1
f	**9**	Br	Cy	80	^{n}Bu$_3$SnH	69	1:1.5

[a] Yields are for isolated chromatographically homogeneous material. [b] Ratios were determined from ^{1}H NMR analysis of total product mixture. [c] SmI_2 (4.5 equiv), THF (40 mL), and HMPA (1.5 mL) per 1 mmol of substrate.

Table 3. Cyclization of Halohydrazones to Cyclohexylhydrazines



entry	substrate	X	R	t, °C	reagent	yield,[a] %	ratio *cis*/*trans*[b]
a	**10**	1	H	–78	SmI_2	53	6:1
b	**10**	1	H	0	SmI_2	43	9:1
c	**10**	1	H	21	SmI_2	62	>15:1
d	**11**	1	Me	21	SmI_2	63	>25:1
e	**12**	2	H	–78	SmI_2	40	>25:1
f	**12**	2	H	21	SmI_2	58	>25:1
g	**13**	2	Me	21	SmI_2	62	>25:1

[a] Yields are for isolated chromatographically homogeneous material. [b] Ratios were determined from ^{1}H NMR analysis of total product mixture. [c] SmI_2 (4.0 equiv), THF (40 mL), and HMPA (1.5 mL) per 1 mmol of substrate.

selective at higher temperatures (Table 3). The 5-exo cyclizations (Table 3, entries a–c) of aldehyde **10** afforded the substituted cyclopentane directly with high diastereoselectivity (>15:1), with the alcohol and hydrazine groups *trans*. In the case of ketone **11**, SmI_2 cyclization gave a single diastereomer (>25:1, none of the other isomer could be observed by ^{1}H NMR). Similar diastereoselective results were achieved with the carbonyl substrates for the cyclohexenyl alcohols (Table 3, entries e–g). The stereochemical preferences (Figure 1) for both the cyclopentanes and the cyclohexanes are consistent with related rationalizations embodying chairlike transition-state models.[4,6c,18] Thus, cyclization from **15** is favored due to the avoidance of the diaxial

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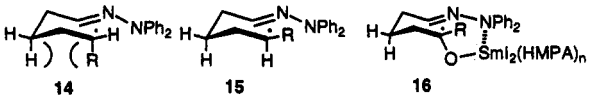
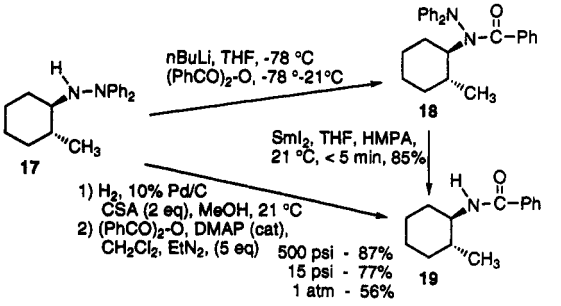


Figure 1. Radical intermediates leading to cyclopentylhydrazides.

Scheme 1. Reductive Cleavage of Hydrazines[a]



[a] No epimerization, similar results for *cis* compounds.

interaction present in **14**. Eight-membered-ring samarium chelates have been invoked previously for related diastereoselective SmI_2 promoted reactions of dicarbonyl compounds.[19] The corresponding nine-membered-ring template **16** allows the large *N*,*N*-diphenyl substituent to adopt a pseudoequatorial orientation, and the axial oxygen helps reduce the gauche interactions en route to the observed products. This stereoselection is similar to those reported for the addition of vanadium ketyls onto conjugated esters.[20]

The synthetic utility of these reactions is further enhanced by conversion of the cyclic hydrazines into amines. This was accomplished in two complementary ways (Scheme 1). Hydrogenolysis[21] (10% Pd/C) furnished the corresponding amines directly (characterized as benzoylamides). Alternatively, for functional groups sensitive to hydrogenation, conversion to the *N*-benzoylhydrazide followed by exposure to SmI_2 provided the amide.[22]

In conclusion, hydrazones are useful radical acceptors for intramolecular cyclizations and hold particular promise for the synthesis of cyclic *trans*-β-amino alcohols as potential glycosidase inhibitors.[23] The extension of these studies to these targets and investigations to utilize the nitrogen radical intermediate in a tandem process are in progress.

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Supplementary Material Available: Experimental procedures for the preparation of all new compounds including spectral data (26 pages). This material is contained in many 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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