Tandem Radical Reactions: Carbon Monoxide Addition to Alkyl Radicals and Subsequent Acyl Radical Cyclization onto *N,N*-Diphenylhydrazones

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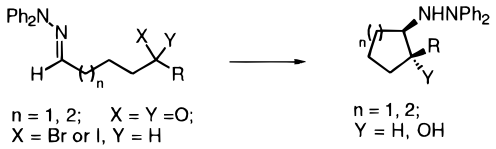
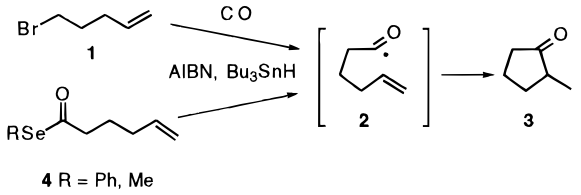
Free-radical cyclizations have received considerable attention in recent years and have been applied to a number of synthetic targets with notable success.[1] A liability inherent in the cyclization of classical radical precursors, such as unsaturated organic halides, is the net loss of the two participating 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, derived from oxathiolanones, to generate products that retain synthetically useful functionality for subsequent manipulation.[2] Atom transfer reactions also place functional groups in predetermined positions.[1c,d,e,f, 3] Alternatively, if a heteroatom is present in the addition terminus the efficiency improves and useful functionality remains in the product. We have recently established that both halo and carbonyl hydrazones cyclize directly to hydrazines under either *n*-Bu_3SnH- or SmI_2-mediated conditions (Scheme 1).[4,5] These reactions display a high level of diastereoselectivity. The carbonylhydrazones provide rapid access to *β*-amino alcohols (a type of intramolecular equivalent of an aza Barbier reaction) after samarium diiodide-mediated hydrazine reduction of the cyclic products. Kinetic studies, based on an intramolecular competition between alkene and hydrazone, revealed the hydrazone cyclization rates were quite rapid.[6] Thus, the 5-*exo* cyclization onto a *N,N*-diphenylhydrazone was approximately 200 times faster than the intramolecular capture by an olefin. These studies have also established that with samarium diiodide these reactions were radical cyclizations and did not involve anionic organosamarium intermediates. We now wish to report that alkyl radicals, generated under tributyltin hydride-mediated conditions from haloprecursors, are trapped efficiently by carbon monoxide. The resultant acyl radicals undergo intramolecular cyclization onto *N,N*-diphenylhydrazones to yield α-hydrazinocyclopentanones. Selective reduction of the parent α-hydrazino ketone provides the corresponding *cis*- or *trans*-*β*-hydrazino alcohols.

Recent years have witnessed an increased interest in the free-radical carbonylation of alkyl radicals. The acyl radicals generated in this manner afford cyclopentanones by intramolecular addition to an alkene or lead to varied products by multicomponent coupling depending upon the nature of reactants selected.[7] Previous studies have demonstrated the utility of a variety of other acyl radical precursors,[8] including selenides, tellurides, cobalt salophens, and *S*-acyl xanthates, which also afford cyclic ketones upon intramolecular addition to alkenes. These cyclic ketones are the major products, and usually decarbonylation does not interfere. Scheme 2 illustrates representative examples of these procedures.

Scheme 1. Radical Cyclizations onto Hydrazones



Scheme 2. Representative Acyl Radical Cyclizations



Recent studies have supplied rate constants for both the addition of carbon monoxide to primary alkyl radicals[7d] and the corresponding decarbonylation reaction. The rate constant for decarbonylation of a secondary acyl radical (3.9×10^5 M^{-1} s^{-1} at 80 °C) is approximately 30 times faster than that for a primary acyl radical,[9] while the rate constants for the trapping of carbon monoxide by primary and secondary radicals are similar (2.7 and 1.2×10^5 M^{-1} s^{-1} at 50 °C, respectively).[7d] The rate constant for the 5-*exo* cyclization of a secondary alkyl radical onto a hydrazone is 1.1×10^8 s^{-1} (80 °C). By analogy, it appeared likely that acyl radical cyclizations onto hydrazones should also be relatively rapid and allow a direct tandem carbonylation−cyclization to yield amino- and alkyl-substituted cyclic ketones upon trapping of the initial alkyl radical by carbon monoxide.

The syntheses of the (*E*)-hydrazones **5-8** are described in the supporting information. The routes involve either alkylation of 1,3-dithiane with the appropriate dibromoalkene, deacetalization, and hydrazine condensation or reduction of *γ*-butyrolactone, hydrazine condensation, oxidation, Grignard addition, and conversion of the resulting secondary alcohols to the corresponding bromides.

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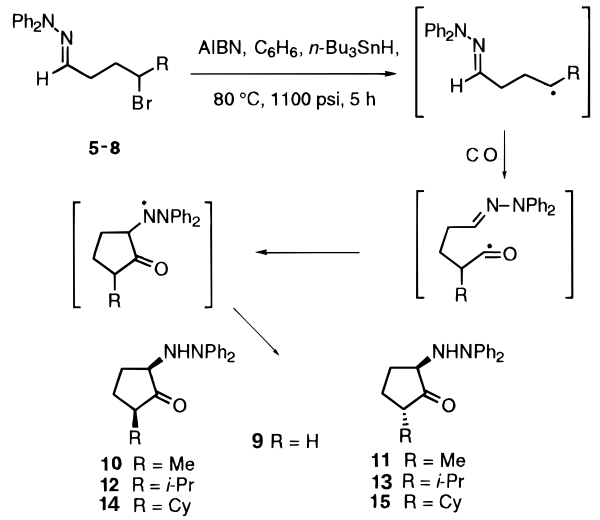
Table 1. Tandem Radical−Carbonylation−Cyclizations

entry	substrate	R	product	yield,[a] %	ratio cis/trans[b]
1	**5**	H	**9**	69	
2	**6**	Me	**10/11**	75	1:1
3	**7**	*i*-Pr	**12/13**	71	1:1.1
4	**8**	Cy	**14/15**	67	1:1.2

[a] Yields are for isolated chromatographically homogeneous material. [b] Ratios were determined from ^{1}H NMR analysis of total product mixture.

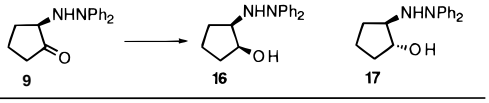
Scheme 3. Carbon Monoxide Trapping and Cyclization onto Hydrazones



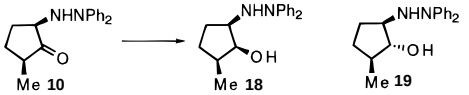
The results of the trapping−cyclization studies are summarized in Table 1, and the products arise from the pathway illustrated in Scheme 3. The desired α-hydazino ketones were produced in reasonable yields but with a disappointing level of stereoselectivity. However, the isomers can be separated readily by flash chromatography. In addition to the ketone products, 10−12% of reduced alkylhydrazone substrates were also isolated. Similar products were observed previously during carbon monoxide-trapping studies of cyclizations onto alkenes.[7b] However, there was no evidence of any aldehyde that would have arisen from direct quenching of the intermediate acyl radical. Both the experimental procedure and the structural assignments of the products were straightforward.[10,11] Neither the yields nor the stereoselectivity of the cyclic ketones were altered significantly upon varying the pressure from 800 to 1100 psi.

In view of the current interest in the synthesis of *β*-amino alcohols as potential glycosidase and chitinase inhibitors,[12] a series of carbonyl reductions to prepare the corresponding hydrazino alcohols were performed. As tabulated (Table 2), ketone **9** (Table 2, entry 4) afforded only the *cis* isomer **16** upon reduction with L-Selectride.[13] In contrast, the *trans* isomer **17** was generated exclusively (Table 2, entry 6) upon hydrogenation of **9** in the presence of tris(triphenylphosphine)ruthenium(II) chloride catalyst.[14] The selectivity of the reductions varied with the substitution pattern of the parent ketone. Thus, the use of L-Selectride also gave the *cis* isomer **18** upon reduction of the ketone **10** (Table 2, entry 7). Mixtures were obtained in the other methyl-substituted cyclopentanone examples; however, the alcohol products were separated cleanly by flash chromatography. Thus, all the possible diastereomers could be prepared depending upon the method selected.

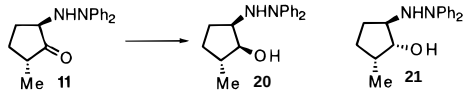
Table 2. Cyclopentanone Reductions



entry	reagent	product	yield,[a] %	ratio cis/trans[b]
1	$(i\text{-Bu})_2$AlH	**16/17**	87%	3:1
2	$Zn(BH_4)_2$	**16/17**	75%	2:1
3	$LiAlH_4$	**16/17**	72%	2.5:1
4	LiB(*s*-Bu$_3$)H	**16/17**	93%	1:0
5	H_2/PtO_2	**16/17**	82%	1:3
6	$H_2/(Ph_3P)_3RuCl_2$	**16/17**	72%	0:1



7	LiB(*s*-Bu$_3$)H	**18/19**	90%	1:0
8	$H_2/(Ph_3P)_3RuCl_2$	**18/19**	71%	1:1



9	LiB(*s*-Bu$_3$)H	**20/21**	82%	1:3
10	$H_2/(Ph_3P)_3RuCl_2$	**20/21**	69%	1:4.5

[a] Yields are for isolated chromatographically homogeneous material. [b] Ratios were determined from ^{1}H NMR analysis of total product mixture.

In conclusion, hydrazones are useful acyl radical acceptors for intramolecular cyclization reactions to afford cyclopentanones[15] in which the initial alkyl radicals are trapped with carbon monoxide. Subsequent ketone reduction provides direct access to the corresponding cyclopentyl *β*-hydrazino alcohols.

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Supporting Information Available: Experimental procedures and compound characterization data (25 pages).

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(10) A 0.05 M benzene solution of hydrazone containing 5−10 mol % AIBN and tributyltin hydride (1.2 equiv) was placed in a glass-lined steel autoclave and heated at 80 °C under an atmosphere of carbon monoxide at a pressure of 1100 psi for 5 h. The autoclave was cooled to 21 °C, the pressure released, and the benzene evaporated. Ether addition followed by a saturated aqueous potassium fluoride wash (4 mL), filtration, drying, and flash chromatography (60/40 dichloromethane/petroleum ether) afforded the cyclopentanone products.

(11) The relative stereochemistries were established by NOE ^{1}H NMR experiments. As has been observed previously, the ^{13}C NMR resonances for both methine carbons in the *cis* isomer appeared at higher field than those for the *trans* isomer.[4] 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. Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633.

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(15) A reviewer has recommended that this study be extended to six-membered rings. However, this would be a rather dubious undertaking as the rate for the 5-*exo* cyclization onto the hydrazone exceeds the rate of addition of a secondary radical onto carbon monoxide by approximately 10^3.