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CO-Trapping Reaction under Thermolysis of Alkoxyamines: Application to the Synthesis of 3,4-Cyclopenta-1-tetralones

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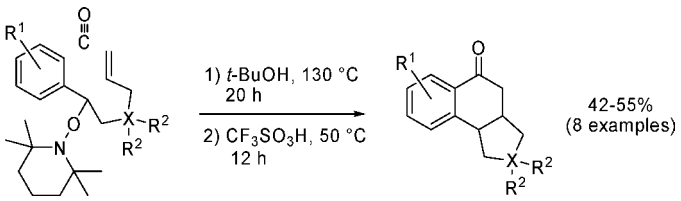
ABSTRACT



An efficient one-pot sequence comprising a PRE-mediated radical 5-*exo*-cyclization, a radical carbonylation, a nitroxide trapping reaction, and a subsequent acid-catalyzed Friedel–Craft-type acylation provides a new entry into 3,4-cyclopenta-1-tetralones. Eight examples are presented.

Over the last few decades, radical chemistry has gained increasing importance in synthetic organic chemistry.[1] While nitroxides are known to efficiently trap radicals to give alkoxyamines, thermally induced reverse homolysis of activated alkoxyamines has recently been recognized as a facile process for the clean generation of C-centered radicals. This unique "go & return" propensity of alkoxyamines led organic chemists to design radical reaction processes based on key basic sequences, which involve (1) the homolysis of alkoxyamines to give carbon radical/nitroxide pairs, (2) radical reactions of the resulting carbon radicals, and (3) recombination of the resulting radicals with nitroxides. In this context, alkoxyamines have been used not only for basic organic transformations[2] but also in iterative reaction processes such as living radical polymerizations.[3] Using TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) and related nitroxides, one of us has previously developed radical cyclization and polymerization reactions which are controlled by the persistent radical effect (PRE).[2,4]

In this paper, we focus on the participation of carbon monoxide[5] in TEMPO-based radical cyclization chemistry.

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(2) (a) Studer, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1108. (b) Marque, S.; Fischer, H.; Baier, E.; Studer, A. *J. Org. Chem.* **2001**, *66*, 1146. (c) Molawi, K.; Schulte, T.; Siegenthaler, K. O.; Wetter, C.; Studer, A. *Chem. Eur. J.* **2005**, *11*, 2335. (d) Studer, A.; Schulte, T. *Chem. Rec.* **2005**, *5*, 27. Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267. Wetter, C.; Jantos, K.; Woithe, K.; Studer, A. *Org. Lett.* **2003**, *5*, 2899. Wetter, C.; Studer, A. *Chem. Commun.* **2004**, 174. Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477. Herrera, A. J.; Studer, A. *Synthesis* **2005**, 1389. Allen, A. D.; Cheng, B.; Fenwick, M. H.; Givehchi, B.; Henry-Riyad, H.; Nikolaev, V. A.; Shikhova, E. A.; Tahmassebi, D.; Tidwell, T. T. Wang, S. *J. Org. Chem.* **2001**, *66*, 2611. Allen, A. D.; Fenwick, M. F.; Henry-Riyad, H.; Tidwell T. T. *J. Org. Chem.* **2001**, *66*, 5759. Leroi, C.; Fenet, B.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 1079.

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Since the cyclopentane-fused tetralone framework represents a key feature of hemigeran-type natural products,[6] we hypothesized that a TEMPO-based radical cyclization−carbonylation sequence would lead to a useful annulation route for preparing such a tricyclic framework (Figure 1).

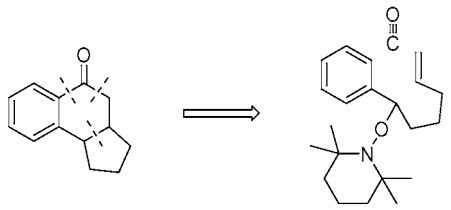
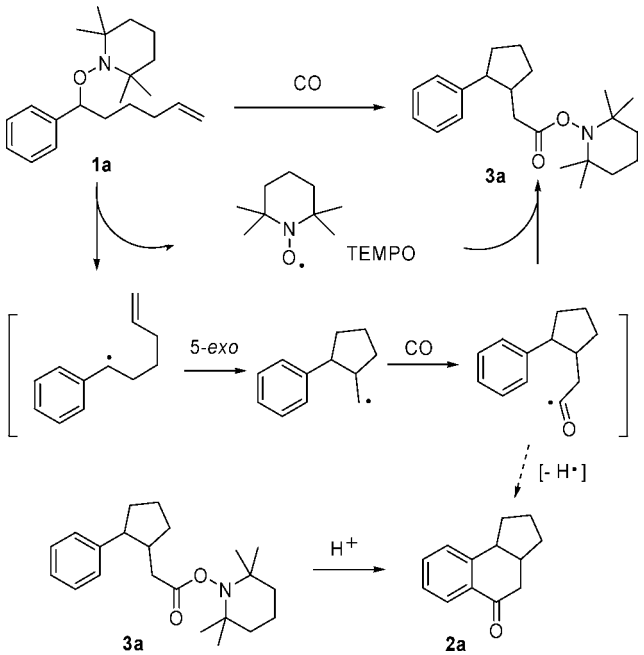


Figure 1.

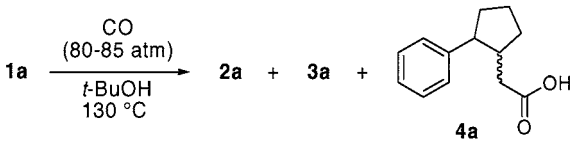
We anticipated that the ultimately formed acyl-TEMPO would resist cleavage back to the acyl radical and TEMPO.[2b] We employed a two-step procedure comprising (1) a PRE-mediated cyclization/carbonylation of 1-phenyl-substituted 5-hexenyloxyamines under thermolysis conditions and (2) an intramolecular Friedel−Crafts-type acylation using Otera's conditions[7] as outlined for the synthesis of 3,4-cyclopenta-1-tetralones in Scheme 1.

Scheme 1. Carbonylation/Acylation Strategy for the Construction of Hemigeran Skeletons



We examined the reaction of 1-phenyl-substituted 5-hexenyloxyamine **1a** under various conditions. When a solution of alkoxyamine **1a** (0.01 M) in *t*-BuOH was heated at 130 °C for 12 h under CO pressure (85 atm), the envisaged acyl-TEMPO product **3a** was formed in 24% yield (Table 1, entry 1). Unexpectedly, carboxylic acid **4a** was found as side

Table 1. Carbonylation of **1a** under Thermal Conditions



entry	**1a** (M)	time (h)	**2a**[a] (%)	**3a**(%) (trans/cis)[b]	**4a**(%) (trans/cis)[b]
1	0.01	12	7	24 (74:26)	14 (68:32)
2	0.01	20	7	trace	46 (69:31)
3[c]	0.01	12	8	trace	45 (70:30)
4	0.05	12	trace	trace	41 (69:31)
5	0.05	20	trace	trace	45 (68:32)

[a] Except for entry 2, yields were determined by ^{1}H NMR. Cis product containing less than 5% of trans isomer was formed. [b] Isolated yields. Cis/trans ratios were determined by ^{1}H NMR. [c] CSA (10 mol %) was added.

product in 14% yield. Probably, acid **4a** derives from **3a** by hydrolysis.[8] Interestingly, the tricyclic product **2a**, the targeted compound, was also identified, albeit in a low yield. The addition of camphor sulfonic acid (CSA),[2a] which promoted the thermal cyclization of **1a** in the absence of CO, failed to improve the yields of carbonylation products in the present case (entry 3). After careful experimentation, we found that the formation of carboxylic acid **4a** as predominant product could be attained at a higher substrate concentration (0.05 M) (entries 4 and 5).

Since the C−O bond of acyl-TEMPO is stable toward homolysis at the temperature employed,[2b] the predominant formation of carboxylic acid **4a** was somewhat surprising. This led us to check the possibility of direct hydrolysis of the initially formed acyl-TEMPO **3a** by *t*-BuOH under the reaction conditions. Indeed, heating of **3a** in *t*-BuOH at 130 °C for 12 h provided **4a** in 94% yield (Scheme 2, eq 1). The mechanism for the hydrolysis is currently not understood. After confirming that carboxylic acid **4a** is most likely obtained via an initially formed acyl-TEMPO **3a** in situ, we next examined the conversion of **3a** and **4a** to the desired benzo fused ketone **2a**. To cyclize carboxylic acid **4a** to tricyclic ketone **2a**, we tested Otera's intramolecular Friedel−Crafts procedure, which involves treatment of the acid with

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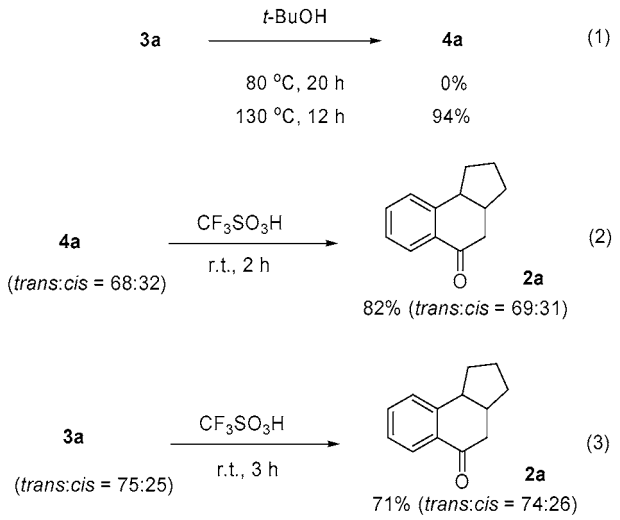
(7) Otera, J.; Orita, A. *Jpn. Kokai Tokkyo Koho* **2000**, 2000−351741.

(8) The acid may be formed from the corresponding *tert*-butyl ester via thermal fragmentation. The *tert*-butyl ester can be formed from acyl-TEMPO **3a** via thermal ketene formation and subsequent trapping of the ketene with *t*-BuOH.

Scheme 2. Hydrolysis and Friedel−Crafts Acylation



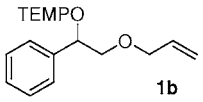
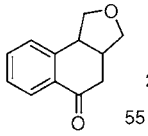
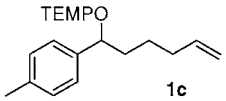
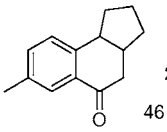
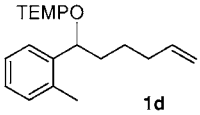
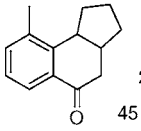
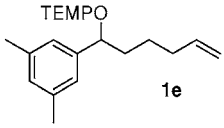
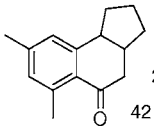
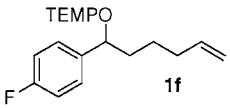
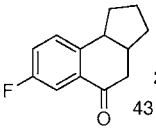
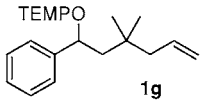
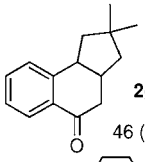
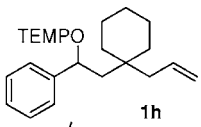
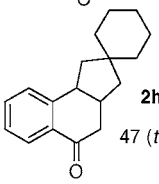
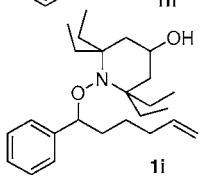
trifluoromethanesulfonic acid (CF_3SO_3H).[7] To our delight, the desired tetralone derivative **2a** was obtained in 82% yield (eq 2). Moreover, we found that treatment of TEMPO-derivative **3a** with CF_3SO_3H under the same conditions also gave tricyclic compound **2a** in 71% (eq 3).

With these results in hand, we examined a sequential process comprising the carbonylation of alkoxyamines under thermal conditions and a subsequent acid promoted cyclization reaction. Table 2 summarizes the synthesis of substituted 3,4-cyclopenta-1-tetralones realized when the sequential procedure was used.

In the first example, after the consecutive reaction, chromatographic separation gave the desired product **2a** in 51% yield. The substrate **1b,** containing an allyl ether moiety also gave the corresponding tetralone derivative bearing a fused THF ring (entry 2, 55%). We also tested substrates **1c**−**e** containing methyl substituents at the phenyl ring. The corresponding cyclopentane-fused tetralone derivatives **2c**−**e** were formed in similar yields (entries 3−5). On the other hand, in the case of substrate **1f**, containing a fluorine atom at the para position, the acid-promoted cyclization was sluggish, requiring an overnight reaction to reach completion (entry 6). A product having a spiro ring was also synthesized using the two step protocol (entry 8). All the tetralones prepared were obtained as trans/cis mixture of isomers. The diastereoisomeric ratio was readily determined by ^{1}H NMR spectroscopy.[9]

The radical cyclization/carbonylations described above require 20 h for completion. We have recently shown that the size of the substituents at the nitroxide moiety heavily influences the reactivity of the alkoxyamines.[2c] With sterically hindered nitroxides highly efficient PRE-mediated processes can be achieved. Therefore, we also tested the reaction of tetraethyl-substituted analogue **1i** (entry 9).

Table 2. Synthesis of 3,4-Cyclopenta-1-tetralones **2** from Alkoxyamines **1** and CO[c]

entry	substrate **1**	product **2**	isolated yield (%)
1	**1a**	**2a**	51 (*trans*:*cis* = 65:35)
2	 **1b**	 **2b**	55 (*trans*:*cis* = 41:59)
3	 **1c**	 **2c**	46 (*trans*:*cis* = 67:33)
4	 **1d**	 **2d**	45 (*trans*:*cis* = 53:47)
5	 **1e**	 **2e**	42 (*trans*:*cis* = 74:26)
6[a]	 **1f**	 **2f**	43 (*trans*:*cis* = 59:41)
7	 **1g**	 **2g**	46 (*trans*:*cis* = 54:46)
8	 **1h**	 **2h**	47 (*trans*:*cis* = 42:58)
9[b]	 **1i**	**2a**	48 (*trans*:*cis* = 63:37)

[a] Friedel−Crafts acylation was conducted over 20 h. [b] Radical carbonylation was performed in 1 h. [c] Conditions: (1) CO (75−80 atm), 130 °C, 20 h; (2) CF_3SO_3H, 50 °C, 2 h.

Indeed, the first cyclization/carbonylation reaction was completed within 1 h. Subsequent acid treatment provided cyclopentane-fused tetralone **2a** in 48% yield. Compared with the analogous TEMPO-mediated process, the reaction time could be shortened; however, a nearly identical yield was obtained.

In summary, the trapping of CO in the thermolysis of 5-alkenyloxyamines represents a new route for tin free radical carbonylation. The carbonylated products can be converted to 3,4-cyclopentatetralones by subsequent treatment with

(9) The unusual *trans* selectivity for the radical 5-*exo* cyclization was previously observed for similar PRE-mediated alkoxyamine isomerizations, see ref 2a. This is probably due to the reversibility of the 5-*exo* cyclization; see: Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6064.

trifluoromethane sulfonic acid. Three consecutive C−C-bond-forming processes are achieved in a one-pot procedure. We are currently exploring some additional efficient alkoxyamine systems that may also be useful in carbonylation reactions and related applications. These studies are currently underway.

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Supporting Information Available: Experimental procedures and analytical data of all new tetralones. This material is available free of charge via the Internet at http://pubs.acs.org.

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