

Lactone Synthesis Based on Atom
Transfer Carbonylation

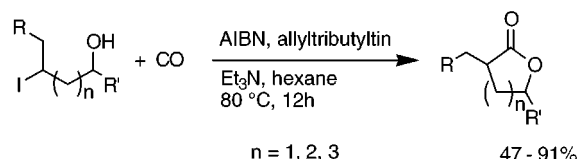
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ABSTRACT



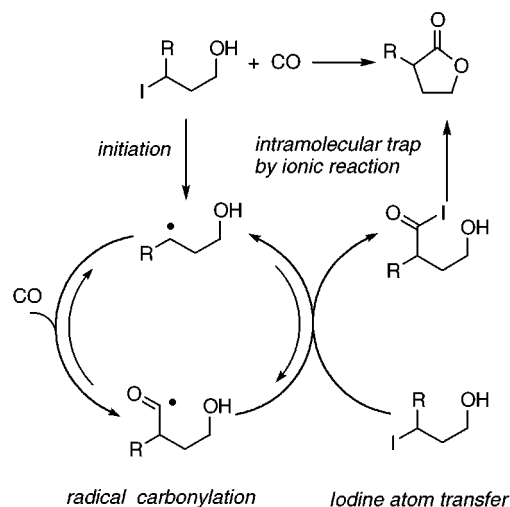
Five- to seven-membered lactones were prepared from ω -hydroxyalkyl iodides and CO by atom transfer carbonylation without the need for transition metal catalysts. The reaction proceeds via a hybrid radical/ionic mechanism in which the intramolecular alcoholysis of an ω -hydroxyacyl iodide, arising from atom transfer carbonylation, leads to the lactone.

Carbonylation reactions represent an important topic in organic synthesis irrespective of whether the species under consideration is an acylmetal or another acyl species such as an acyl radical.¹ Regarding the synthesis of lactones by carbonylation, a number of metal-catalyzed systems have been reported thus far.^{2–4,5}

During the course of our studies in the development of nontransition metal-based carbonylation methods,^{1b,c} we recently reported that atom transfer carbonylation, combined with a judicious choice of both the radical initiation system and the subsequent ionic quenching sequence, provides a route to carboxylic acid esters and amides from alkyl iodides and CO.⁶ In this Letter we report on an intramolecular variation of a similar atom transfer carbonylation starting

with ω -hydroxyalkyl iodides which leads to a novel method for the synthesis of five- to seven-membered ring lactones. As can be seen from the strategy in Scheme 1, the envisaged protocol for lactone synthesis consists of three basic steps:

Scheme 1. A Radical/Ionic Hybrid Approach for the Synthesis of Lactones

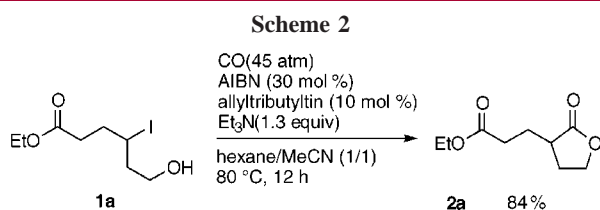


(1) (a) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum: New York, 1991. For reviews on radical carbonylation, see: (b) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (c) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (d) Chatgililoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(2) For examples of transition metal-catalyzed carbonylation of vinyl and aryl halo alcohols leading to lactones, see: (a) Aoyagi, S.; Hasegawa, Y.; Hirashima, S.; Kibayashi, C. *Tetrahedron Lett.* **1998**, *39*, 2149. (b) Luo, F.-T.; Wang, M.-W.; Liu, Y.-S. *Heterocycles* **1996**, *43*, 2725. (c) Suzuki, T.; Uozumi, Y.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1593. (d) Martin, L. D.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 3630. (e) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193. (f) Mori, M.; Chiba, K.; Inotsume, N.; Ban, Y. *Heterocycles* **1979**, *12*, 921.

(i) radical carbonylation, (ii) iodine atom transfer, and (iii) *intramolecular* ionic quenching of the generated acyl iodide to afford the lactone, shifting the two reversible radical steps (Scheme 1).⁷

Typically, 3-hydroxyalkyl iodide **1a** (145.9 mg, 0.5 mmol) was placed in a 50 mL stainless steel autoclave, lined with a glass liner, with AIBN (24.6 mg, 0.15 mmol) and allyltributyltin (16.6 mg, 0.05 mmol) as the radical initiator,^{6b} along with a mixture of hexane and MeCN (0.3 mL of each) as solvent and Et₃N (65.8 mg, 0.65 mmol) as base. The autoclave was closed, purged twice with CO, pressurized with 45 atm of CO, and then heated with stirring at 80 °C for 12 h. Excess CO was discharged at room temperature after the reaction. Washing the crude mixture with MeCN (5 mL) followed by precipitation of the NHET₃⁺I⁻ in ether (50 mL), filtration, evaporation of the filtrate, and column chromatography on silica gel (ether–hexane; 0–30%) gave γ -lactone **2a** in 84% yield (Scheme 2).



Some additional data on lactone syntheses are summarized in Table 1. Using this method, γ -lactones were prepared generally in good yields from the corresponding 3-iodo alcohols and carbon monoxide (runs 1–7). Hydroxyalkyl iodides which contain a perfluoroalkyl group in the β position to the iodine-attached carbon worked well for this lactone synthesis (runs 2, 5, and 7). Presumably due to the lower propensity for iodine atom transfer, the conversion of the primary alkyl iodide **1d** to lactone **2d** was slow (75% conversion after 24 h, run 4). This resulted in the formation of 2-ethyl-3-propyloxetane (11%) as a byproduct, which likely arises via the S_N2 type ring closure of **1d**. One example

(3) For recent examples of transition metal-catalyzed carbonylation of unsaturated alcohols leading to lactones, see: (a) Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1999**, *121*, 7708. (b) Ogawa, A.; Kawabe, K.; Kawakami, J.; Mihara, M.; Hirao, T. *Organometallics* **1998**, *17*, 3111. (c) Brunner, M.; Alper, H. *J. Org. Chem.* **1997**, *62*, 7565. (d) Ukaji, Y.; Miyamoto, M.; Mikuni, M.; Takeuchi, S.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 735.

(4) For lactone synthesis by the Pd-catalyzed carbonylation of perfluoroalkyl iodides, see: Urata, H.; Yugari, H.; Fuchikami, T. *Chem. Lett.* **1987**, 836.

(5) We have recently developed a new route for the synthesis of δ -lactones by oxidative radical carbonylation of saturated alcohols, see: (a) Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 8962. (b) Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* **1994**, *116*, 5473.

(6) (a) Nagahara, K.; Ryu, I.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1997**, *119*, 5465. (b) Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* **1998**, 1953.

(7) A hybrid radical/ionic system is also useful for atom transfer reactions other than carbonylation, see: (a) Joung, M. J.; Ahn, J. H.; Lee, D. W.; Yoon, N. M. *J. Org. Chem.* **1998**, *63*, 2755. (b) Curran, D. P.; Ko, S.-B. *Tetrahedron Lett.* **1998**, *39*, 6629.

Table 1. Lactone Synthesis via Atom Transfer Carbonylation^a

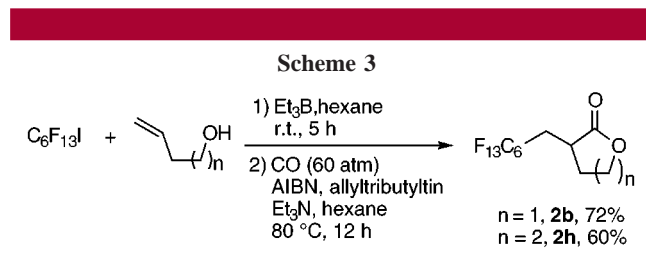
run	ω -iodo alcohol 1	1) [1] 2) CO 3) solvent	product 2	yield (%) ^b (cis/trans)
1		1) 1.7 M 2) 45 atm 3) hexane/MeCN (1/1)		84
2		1) 2.5 M 2) 45 atm 3) hexane		81
3		1) 1.2 M 2) 60 atm 3) hexane		84 (64/36)
4 ^c		1) 3.0 M 2) 90 atm 3) hexane		47 ^d (53/47)
5		1) 1.1 M 2) 45 atm 3) hexane		71 (49/51)
6 ^e		1) 1.4 M 2) 80 atm 3) hexane		64 ^f
7		1) 2.0 M 2) 45 atm 3) hexane		91 (37/63)
8		1) 1.7 M 2) 60 atm 3) hexane		63
9		1) 1.7 M 2) 60 atm 3) hexane		58

^a General reaction conditions: **1** (0.5–1.0 mmol), AIBN (0.2–0.3 equiv), allyltributyltin (0.1 equiv), Et₃N (1.3 equiv), solvent (0.3–0.7 mL), CO (45–90 atm), 80 °C, 12 h. ^b Yields after isolation by chromatography on silica gel. ^c Reaction time: 24 h. ^d 75% conversion. ^e Xe lamp irradiation was used for the initiation; reaction time 22 h. ^f ¹H NMR yield.

shows that photoirradiation conditions^{6a} can be used for the lactone synthesis in place of a thermal initiator (run 6). The scope of this synthetic strategy was extended successfully to the synthesis of six- and seven-membered lactones as well (runs 8 and 9).

Some of the substrates used in this study were prepared by the carboiodination of olefinic alcohols,⁸ and this led us to examine a more concise procedure for the synthesis of lactones. Thus, fluoroalkyl-substituted lactones **2b** and **2h** can be prepared from the corresponding alkenol and per-

fluorohexyl iodide without the need to isolate compounds **1b** and **1h**, respectively (Scheme 3).⁹



In summary, we have presented herein a new carbonylation method for the synthesis of lactones from ω -hydroxyalkyl iodides and CO which does not require transition metal catalysts. Further applications to other atom transfer carbonylation/ionic reaction sequences are currently being investigated in our laboratory.

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Supporting Information Available: Spectroscopy data and analytical data of compounds **2a–2i**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(8) **1b**, **1e**, **1g**, **1h**, and **1i** were prepared by carboiodination of the respective olefinic alcohols, see: Takeyama, Y.; Ichinose, Y.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 3159. **1a** was prepared by photoirradiation of a mixture (1/5/0.04) of ethyl iodoacetate, 3-buten-1-ol, and $\text{Pd}(\text{PPh}_3)_4$. **1c** and **1f** were prepared by the reaction of 2-ethyl-1,3-hexanediol and 1,3-butanediol, respectively, with diiodosilane, see: Keinan, E.; Perez, D. *J. Org. Chem.* **1987**, *52*, 4846. **1d** was prepared from the same precursor as **1c** by using a standard MsCl/NaI reaction.

(9) For a similar reaction with the use of a Pd catalyst, see ref 4.