

## Free Radical Mediated Double Carbonylations of Alk-4-enyl Iodides

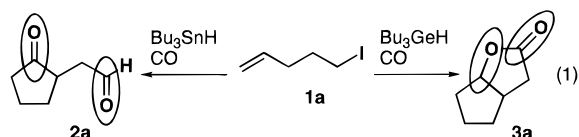
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Over the past decade tandem processes based on free radical methods have gained increasing importance in organic synthesis, since they allow for the simultaneous formation of more than one bond in a single synthetic operation from relatively simple precursors.<sup>1</sup> Carbon monoxide also participates in such tandem free radical reactions as a useful C<sub>1</sub> radical acceptor/donor synthon.<sup>2</sup>

In this paper, we report the synthetic potential of a double CO-trapping reaction by pent-4-enyl radicals that starts with pent-4-enyl iodides. Interestingly, we found that the major products obtained via double CO trapping are dependent on the radical mediator used. The tin hydride mediated system afforded the anticipated keto aldehyde **2**, and surprisingly, the germyl hydride mediated system afforded the bicyclic  $\gamma$ -lactone **3** as the principal double CO incorporation product (eq 1).



Reaction of pent-4-enyl radical and CO would be expected to yield hex-5-enyl radical (**A**) as the initial intermediate (Scheme 1). The subsequent 5-*exo* cyclization of radical **A** generates 3-oxocyclopentyl carbonyl radical (**B**), which rapidly isomerizes to the thermodynamically more stable 3-oxocyclohexyl radical (**C**).<sup>3</sup> We anticipated that, under high CO concentrations, the kinetic radical **B** would be trapped by a second molecule of CO, in preference to isomerization leading to **C**. As we had envisioned, we have successfully developed the procedure to obtain five-membered cyclic 4-keto aldehydes in reasonable yields. For example, when the AIBN-initiated reaction of pent-4-enyl iodide with tributyltin hydride (1.2 equiv) was carried out under 90 atm of CO (0.01 M in benzene, 80 °C, 3 h), 2-(2-oxoethyl)cyclopentanone (**2a**), the anticipated double carbonylation product, was obtained in 42% yield after

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(1) For leading reviews, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417, 489. (c) Motherwell, W. B.; Crich, D. *Best Synthetic Methods, Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, Chapters 4.1 and 4.2.

(2) For reviews, see: (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, 96, 177. (b) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 1050.

(3) (a) Luszyk, J.; Luszyk, E.; Maillard, B.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, 106, 2923. (b) Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1018. (c) Ballestri, M.; Chatgililoglu, C.; Cardì, N.; Sommazzi, A. *Tetrahedron Lett.* **1992**, 33, 1787. (d) Riemann, H.; Capomaggi, A. S.; Strauss, T.; Oliveto, E. P.; Barton, D. H. R. *J. Am. Chem. Soc.* **1961**, 83, 4481. (e) Gimisis, T.; Ballestri, M.; Ferreri, C.; Chatgililoglu, C. *Tetrahedron Lett.* **1995**, 36, 3897. Also see (a review): (f) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, 93, 2091. (g) Chatgililoglu, C.; Ferreri, C.; Sommazzi, A. *J. Am. Chem. Soc.* **1996**, 118, 7223.

Table 1. Double Carbonylations of Alk-4-enyl Iodides

| run | RI | R <sub>3</sub> MH <sup>a</sup>        | keto aldehyde <b>2</b> , % <sup>b</sup> | $\gamma$ -lactone <b>3</b> , % <sup>b</sup> |
|-----|----|---------------------------------------|---|---|
| 1   | 1a | Bu <sub>3</sub> SnH                   | 2a 44, 42, <sup>c</sup> 70 <sup>d</sup> | 3a 0  |
| 2   |    | (Me <sub>3</sub> Si) <sub>3</sub> SiH | 12                                      | 19  |
| 3   |    | Bu <sub>3</sub> GeH                   | 6                                       | 27  |
| 4   | 1b | Bu <sub>3</sub> SnH                   | 2b 40 (62/38) <sup>e</sup>              | 3b 0  |
| 5   |    | Bu <sub>3</sub> GeH                   | 6                                       | 26 (63/37) <sup>f</sup>                     |
| 6   | 1c | Bu <sub>3</sub> SnH                   | 2c 45                                   | 3c 0  |
| 7   |    | Bu <sub>3</sub> GeH                   | 12                                      | 40  |
| 8   | 1d | Bu <sub>3</sub> SnH                   | 2d 33                                   | 3d 0  |
| 9   |    | Bu <sub>3</sub> GeH                   | 9                                       | 29  |
| 10  | 1e | Bu <sub>3</sub> SnH                   | 2e 47 (38/62) <sup>f</sup>              | 3e 6  |
| 11  |    | Bu <sub>3</sub> GeH                   | 7                                       | 29 (50/50) <sup>f</sup>                     |
|     |    |                                       |   | 3e' 13                                      |
| 12  | 1f | Bu <sub>3</sub> SnH                   | 2f 40 (43/57) <sup>f</sup>              | 3f 4  |
| 13  |    | Bu <sub>3</sub> GeH                   | 1                                       | 30 (42/58) <sup>f,g</sup>                   |

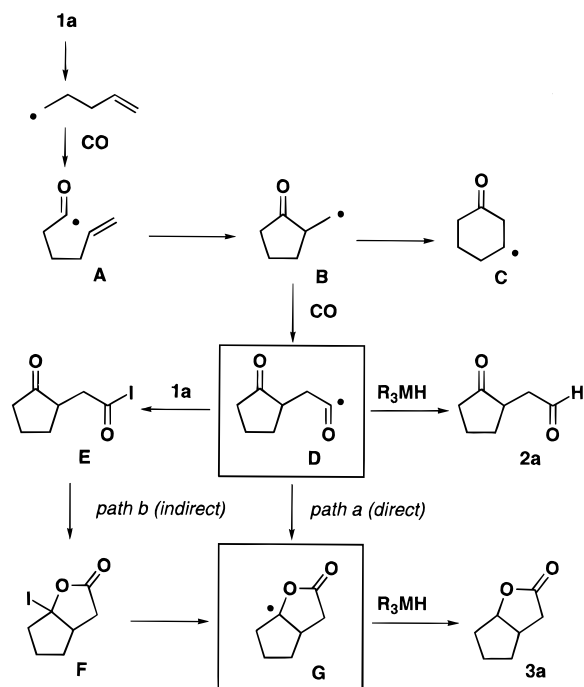
<sup>a</sup> M = Sn: 0.01 M in benzene, Bu<sub>3</sub>SnH (1.2 equiv), AIBN (0.1 equiv), CO (90 atm), 70–80 °C, 3–4 h. M = Si: 0.01 M in benzene, TTMS (1.1 equiv), AIBN (0.35 equiv), CO (90 atm), 80 °C, 5 h. M = Ge: 0.06–0.2 M in benzene, Bu<sub>3</sub>GeH (1.5 equiv), AIBN (0.3–0.5 equiv), CO (90 atm), 70–100 °C, 16 h (see the Supporting Information). <sup>b</sup> Isolated yields purified by preparative HPLC. <sup>c</sup> Isolated yield purified by silica gel chromatography. <sup>d</sup> GC yield. <sup>e</sup> Ratio of *cis/trans* was determined by GC. <sup>f</sup> Ratio of *endo/exo* or *cis/trans* was determined by <sup>1</sup>H NMR. <sup>g</sup> Unsaturated  $\gamma$ -lactone was also formed (<2%).

isolation by flash chromatography on silica gel.<sup>4</sup> This double CO-trapping reaction, which gives rise to the keto aldehydes **2**, appears to be a general reaction, and secondary iodides function as well as primary iodides (Table 1, runs 1, 4, 6, 8, 10, and 12).

When tributylgermyl hydride was used as the radical mediator in the reaction of **1a**, we were surprised to observe the formation of the bicyclic  $\gamma$ -lactone 2-oxabicyclo[3.3.0]octan-3-one (**3a**) (Table 1, run 3). This lactone is an isomer of keto aldehyde **2a**, since two molecules of CO were incorporated as the C–O–C=O linkage of the lactone ring. No **3a** was produced

(4) Experimental details are provided in the Supporting Information. The yields of this reaction require optimization: Single carbonylation products constitute main byproducts, and a small amount of six-membered double carbonylation products were also detected (1–4%).

Scheme 1



on exposure of 4-keto aldehyde **2a** to the original carbonylation conditions ( $\text{Bu}_3\text{GeH}/\text{CO}$ ). This germyl hydride mediated reaction is also quite general, and in all six cases examined, which include primary and secondary alk-4-enyl iodides, we obtained the corresponding bicyclic  $\gamma$ -lactones **3a–f** without exception, in one case isolating significant amount of unsaturated lactone **3e'** (Table 1, runs 3, 5, 7, 9, 11, and 13).

Control experiments were carried out to gain some insights into the mechanism for this unusual lactone formation. To obtain more favorable bicyclic lactone/keto aldehyde ratios, the choice of a "slower" radical mediator such as tributylgermane is crucial.<sup>5</sup> Tris(trimethylsilyl)silane (TTMSS),<sup>6</sup> a slower mediator than tributyltin hydride and a faster mediator than tributylgermane, gave intermediate results (Table 1, run 2). Raising the ratio of  $\text{Bu}_3\text{GeH}$  to **1a** suppressed the formation of lactone **3a** and increased the relative amounts of keto aldehyde **2a**. These observations are consistent with the assumption that the formation of lactone **3a** is due to a rare 5-*endo* cyclization of the acyl radical **D**,<sup>7</sup> arising from the second CO trapping by **B**, onto the carbonyl oxygen to afford **G** (Scheme 1, path a), which would compete with intermolecular hydrogen abstraction from tributylgermane thus leading to **2a**. On the other hand,

(5) Tributylgermyl hydride is a poorer hydrogen donor to alkyl radicals than tributyltin hydride, see: Johnston, L. J.; Luszyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594.

(6) Chatgililoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

(7) Rare examples of 5-*endo* cyclizations of acyl radicals are restricted to cyclizations onto conjugated carbonyls. For recent examples, see: (a) Mendenhall, G. D.; Protasiewicz, J. D.; Brown, C. E.; Ingold, K. U.; Luszyk, J. *J. Am. Chem. Soc.* **1994**, *116*, 1718, 5525. (b) Yamamoto, Y.; Ohno, M.; Eguchi, S. *J. Am. Chem. Soc.* **1995**, *117*, 9653.

other data collected on this system are not entirely consistent with this simplified scenario. Dilution failed to increase the product ratio of **3a** to **2a** in favor of an intramolecular reaction course leading to **3a**. Furthermore, the corresponding pent-4-enyl bromide yielded only a trace amount of **3a** when exposed to standard  $\text{Bu}_3\text{GeH}/\text{CO}$  conditions such as, for example, run 3 in Table 1. These observations suggest that an iodine atom transfer reaction may play an important role in this  $\gamma$ -lactone ring formation. One possible rationale may involve an iodine transfer reaction from alkyl iodide **1a** to acyl radical **D** to give acyl iodide **E**,<sup>8</sup> which might be permitted by a slow mediator system involving  $\text{Bu}_3\text{GeH}$ , and the cyclization of the resulting **E** to yield **F** (path b, Scheme 1).<sup>9</sup> Although iodine transfer from an alkyl iodide to an acyl radical may be regarded as an energetically unfavored process, the intermediacy of **E** in this reaction system is a reasonable suggestion, based on indirect evidence.<sup>10</sup>

Thus, through this study, we have demonstrated an easy access to two fascinating free radical intermediates, five-membered cyclic 4-keto acyl radicals and bicyclic  $\gamma$ -lactone radicals, from readily available alk-4-enyl iodides and CO. Work in this area is currently underway and includes tandem applications of these free radical intermediates as well as the precise evaluation for the cyclization mechanism.

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**Supporting Information Available:** Control experiments and compound characterization data for all products (33 pages). See any current masthead page for ordering and Internet access instructions.

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(8) Even with the use of  $\text{Bu}_3\text{SnH}$ , secondary iodides **1e** and **1f** gave lactones **3e** and **3f** as minor products, respectively (runs 10 and 12). This may be related to the known fact that secondary iodides are more prone to undergo atom transfer than primary iodides. (a) Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195. Also see: Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140 and references cited therein.

(9) To the best of our knowledge, we are not aware of any precedent for this type of atom transfer reaction. Ab initio calculations (3-21G\*) show that iodine atom transfer from alkyl iodide to acyl radical is energetically unfavorable ( $\Delta H = 4.83$  kcal/mol for primary alkyl iodide, 1.92 kcal/mol for secondary alkyl iodide). As one possibility, we suspect that the subsequent conversion of acyl iodide **E** to the pseudoacid iodide **F** might be sufficiently smooth to override this energetic disadvantage. For this cyclization step, a single electron transfer from acyl iodide to internal ketone carbonyl, followed by the coupling of the resulting ion pair or a spontaneously ionic path might be possible. Cf.: Heathcock, C. H.; Davidsen, S. K.; Mills, S. G.; Sanner, M. A. *J. Org. Chem.* **1992**, *57*, 2531.

(10) The reaction of **1a** with  $\text{Bu}_3\text{GeH}/\text{CO}$  in ethanol and potassium carbonate gave the corresponding 4-keto ester in 21% yield. For details, see the Supporting Information. As for the formation of **F**, the detection of a small amount of unsaturated lactone **3e'** in the case of secondary iodide **1e**, may document the existence of **F** in this reaction system. For mechanistic discussion on related transformations, see: (a) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119. (b) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343. (c) Beckwith, A. L. J.; Storey, J. M. *D. J. Chem. Soc., Chem. Commun.* **1995**, 977.