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Communications

Double Alkylation of Carbon Monoxide via Free Radicals: Synthesis of Unsymmetrical Ketones

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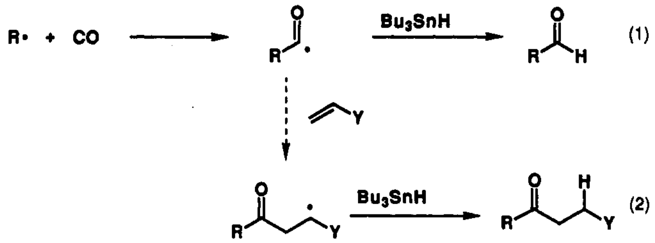
Summary: A novel method for the synthesis of unsymmetrical ketones via the *free radical carbonylation* of alkyl halides is described. The mechanism of the reaction involves the trapping of an alkyl free radical by CO, the addition of the acyl free radical so formed to an alkene, and termination of the reaction by the abstraction of a hydrogen atom from tributyltin hydride by the product acyl-substituted free radical.

Directly attaching two different carbon chains to carbon monoxide represents, in theory, an attractive means of preparing unsymmetrical ketones. Recently we[1] reported the first successful *free radical carbonylation* of alkyl halides to give aldehydes. Both the trapping of the alkyl free radical by CO and the subsequent abstraction of a hydrogen atom from tributyltin hydride by the product acyl radical took place efficiently (eq 1). If an alkene is also present, at least two other reactions would be expected to take place: (i) the direct addition of the alkyl free radical to the alkene[2] and (ii) the trapping of the alkyl free radical by CO to form an acyl free radical and the subsequent addition of that radical to the alkene.[3] If the latter reaction predominates, a double alkylation of carbon monoxide, leading to an unsymmetrical ketone, would be accomplished (eq 2). Because it has been established[4,5] that alkyl free radicals often add to alkenes at a slower rate than they abstract a hydrogen atom from tributyltin hydride, we believed that, even in a system that contained an alkene, trapping of the alkyl free radical by CO would predominate over direct addition of that radical to the alkene. We describe herein a free radical method for synthesizing unsymmetrical ketones by the reaction of CO, an alkyl halide, and an alkene in the presence of tributyltin hydride.[6]



In a typical experiment, a benzene solution of hexyl iodide (**1a**, 0.75 mmol, 0.05 M), n-Bu$_3$SnH (1.05 mmol),

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[1] Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 1295.

[2] For reviews on the addition of free radicals to alkenes, see: (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753; (b) **1985**, *24*, 553; (c) **1989**, *28*, 969.

[3] For earlier work on the addition of aldehydes to alkenes via acyl radical intermediates, see: (a) Kharasch, M. S.; Urry, W. H.; Kuderna, B. M. *J. Org. Chem.* **1949**, *14*, 248. (b) Urry, W. H.; Huyser, E. S. *J. Am. Chem. Soc.* **1953**, *75*, 4876. (c) Partrick, T. M., Jr. *J. Org. Chem.* **1952**, *17*, 1009, 1269. For a recent report describing the use of acyl selenides as acyl radical precursors, see: (d) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1989**, *54*, 1777 and references cited therein.

[4] (a) Citterio, A.; Arnoldi, A.; Minisci, F. *J. Org. Chem.* **1979**, *44*, 2674. (b) Giese, B.; Kretzschmar, G. *Chem. Ber.* **1983**, *116*, 3267. (c) Giese, B.; Kretzschmar, G. *Chem. Ber.* **1984**, *117*, 3160. (d) Curran, D. P.; van Elburg, P. A.; Giese, B.; Gilges, S. *Tetrahedron Lett.* **1990**, *31*, 2861 and footnote 16.

[5] Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* 1981, *103*, 7739.

[6] A portion of this work has been presented at 37th Symposium on Organometallic Chemistry, Osaka, Japan, October 27, 1990. Very recently, free radical cyclizations that use an isonitrile as a C$_1$ unit have been reported, see: Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127.

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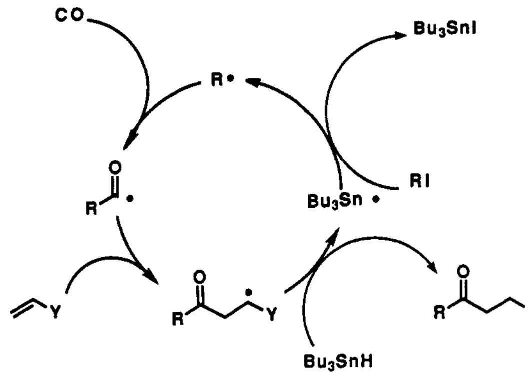
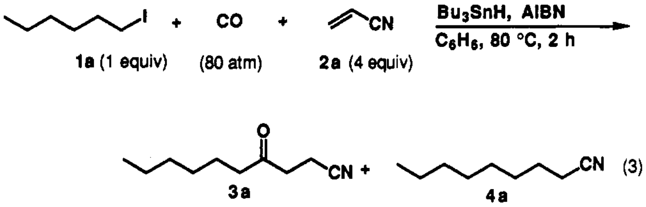
Scheme I



acrylonitrile (**2a**, 3 mmol), and AIBN (0.1 mmol) under 80 atm of CO was heated at 80 °C for 2 h (eq 3).[7] Flash chromatography of the crude product mixture on silica gel (hexane/Et$_2$O, 9:1) gave the desired β-cyanoethyl hexyl ketone (**3a**) (R_f = 0.2) in 44% yield. Octyl cyanide (**4a**) (R_f = 0.5) was also isolated, in 37% yield.

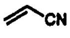
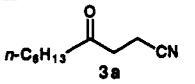
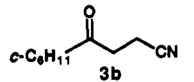
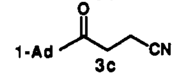
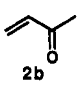
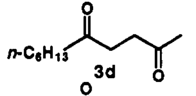
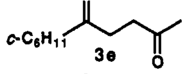
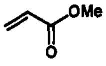
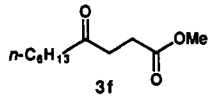
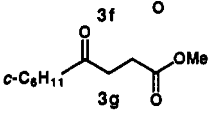
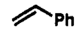
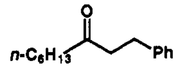
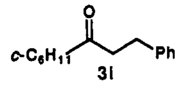
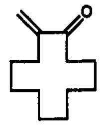
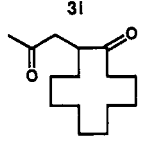


(3)

	3a	4a
$[1a]_0$ = 5.0X10^{-2} M	44%	37%
2.5X10^{-2}	60%	24%
1.7X10^{-2}	74%	9%

The formation of cyanoethyl hexyl ketone can be explained in terms of a free radical chain propagation mechanism (Scheme I). The stannyl free radical, generated by abstraction of a hydrogen atom from tributyltin hydride by the cyanopropyl free radical (derived from AIBN), abstracts an iodine atom from hexyl iodide to give the hexyl free radical, which then is trapped by carbon monoxide. The resulting heptanoyl free radical adds to acrylonitrile. The cyanoalkyl free radical thus formed abstracts a hydrogen atom from tributyltin hydride to give the desired ketone and, coincidentally, regenerates the stannyl free radical. Octyl cyanide is formed as a result of the competing addition of the hexyl free radical to acrylonitrile. Performing the reaction under conditions of *high dilution* proved to be very effective in suppressing the addition of the hexyl free radical to acrylonitrile. Under such conditions, the concentration of the heptanoyl free radical would be expected to be higher than that of the hexyl free radical because the concentration of *dissolved* CO would remain unchanged. Indeed, the cyano ketone/cyanoalkane (**3a**/**4a**) ratio increased dramatically, from 1.2 to 8.2, when the initial concentration of hexyl iodide was decreased from 0.05 to 0.017 M. The results of the reaction of CO with other alkyl halides[8] and alkenes, performed under conditions of high dilution,[9] are summarized in Table I.

Table I. Synthesis of Unsymmetrical Ketones by the Reactions of RX, CO, an Alkene, and n-Bu$_3$SnH[a]

run	RX	alkene	product (yield,[b] %)
1	n-C$_6$H$_{13}$I 1a	 2a	 3a (74)
2	c-C$_6$H$_{11}$I 1b	2a	 3b (60)
3[c]	1-Ad-I 1c	2a	 3c (46)
4	1a	 2b	 3d (68)
5	1b	2b	 3e (57)
6	1a	 2c	 3f (59)
7	1b	2c	 3g (40)
8	1a	 2d	 3h (36)
9	1b	2d	 3i (33)
10[d]	MeI 1d	 2e	 3j (40)[e]

[a] Unless otherwise noted, reactions were performed with 0.017 M solutions of **1** contained in a stainless steel autoclave lined with a round-bottomed glass tube. Conditions: **1** (0.75 mmol), **2** (3 mmol), n-Bu$_3$SnH (1.05 mmol), AIBN (0.1 mmol), C$_6$H$_6$ (45 mL), CO (75–80 atm), 80 °C, 2–3 h. [b] Yield of pure products isolated by flash chromatography on silica gel. [c] $[1c]_0$ = 1.2 × 10^{-2} M. [d] Conditions: **1d** (4.6 mmol), **2e** (0.94 mmol), n-Bu$_3$SnH (2.0 mmol), AIBN (0.18 mmol), C$_6$H$_6$ (45 mL), CO (80 atm), 80 °C, 3 h. [e] No attempt was made to optimize the yield (unreacted **2e** was recovered).

The reaction of CO, hexyl iodide (**1a**), and methyl vinyl ketone (**2b**), in the presence of Bu$_3$SnH, gave undecane-2,5-dione (**3d**), a precursor of dihydrojasmone,[10] in 68% yield after purification by flash chromatography. The use of methyl acrylate (**2c**) in place of methyl vinyl ketone afforded the corresponding 4-keto ester **3f** in 59% yield. Less reactive styrene (**2d**) could also serve as the acyl

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[7] When 2 equiv of acrylonitrile were used, significant amounts of heptanal were formed. This result implies that the heptanoyl free radical abstracts a hydrogen atom from n-Bu$_3$SnH more rapidly than it adds to acrylonitrile.

[8] Alkyl bromides can also serve as sources of alkyl free radicals. However, they are less reactive than alkyl iodides, especially under conditions of high dilution.

[9] The following procedure is typical. A mixture of benzene (45 mL), 1-iodohexane (**1a**; 159 mg, 0.75 mmol), n-Bu$_3$SnH (365 mg, 1.05 mmol), AIBN (16 mg, 0.1 mmol), and acrylonitrile (**2a**; 160 mg, 3.0 mmol) was placed in a 100-mL stainless steel autoclave lined with a round bottomed glass tube. The autoclave was then pressurized with 80 atm of CO and was heated, with stirring, at 80 °C for 2 h. After the excess CO was discharged at room temperature, the benzene was evaporated (rotary evaporator). The residue was dissolved in Et$_2$O (5 mL). The ethereal solution was then treated with saturated aqueous KF. The n-Bu$_3$SnF that was precipitated was removed by vacuum filtration. The solid was washed with Et$_2$O (3 × 5 mL). The two liquid layers were separated. The organic layer was dried (MgSO$_4$) and concentrated. The residue, a colorless oil, was purified by flash chromatography on silica gel (Et$_2$O/hexane, 1:9). The major fraction eluted from the column contained 92.7 mg (74%) of 1-cyano-3-nonanone (**3a**). The minor fraction contained 9.4 mg (9%) of octyl cyanide (**4a**).

[10] Stetter, H.; Kuhlman, H.; Haese, W. *Org. Synth.* **1987**, *65*, 26.

radical acceptor. It gave 1-phenyl-3-nonanone (**3h**). On the other hand, electron-rich olefins like vinyl butyl ether failed to react, a result that is consistent with the nucleophilic nature of the addition of acyl radicals to olefins.[3] Heptanal, which arose from carbonylation of the hexyl free radical, was the major product in such cases. Secondary alkyl iodides also were reactive (runs 2, 5, 7, 9). However, even under conditions of high dilution ($[\mathbf{1c}]_0 = 0.012$ M), the greater tendency—compared to primary and secondary alkyl free radicals—of the adamantyl free radical to add to olefins[11] rather than undergo carbonylation led to a low yield of ketone **3c** (run 3). 2-Methylenecyclododecanone (**2e**) could also serve as the acyl radical acceptor. The reaction of CO, methyl iodide, and **2e** gave 2-acetonylcyclododecanone (**3j**) (run 10).[12]

Thus, a double alkylation of carbon monoxide via free radicals, which leads to unsymmetrical ketones, has been achieved. The use of free radical reactions in organic synthesis is now receiving considerable attention because such use is compatible with the presence of a variety of organic functional groups. In this respect, the benefits that can be realized by the use of *free radical carbonylation* are undoubtedly large. Additional applications of the reaction are now being investigated in our laboratory.

Supplementary Material Available: Detailed experimental procedures and the physical characteristics of the products (6 pages). Ordering information is given on any current masthead page.

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[11] The nucleophilicity of the 1-adamantyl free radical has been described. See: Ohno, M.; Ishizaki, K.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 1285.

[12] This compound is a key intermediate in the synthesis of muscone and exaltone, see: Tsuji, J.; Yamada, T.; Shimizu, I. *J. Org. Chem.* **1980**, *45*, 5209.

First Total Synthesis of Amaryllidaceae Alkaloids of the 5,11-Methanomorphanthridine Type. An Efficient Total Synthesis of (±)-Pancracine[1]

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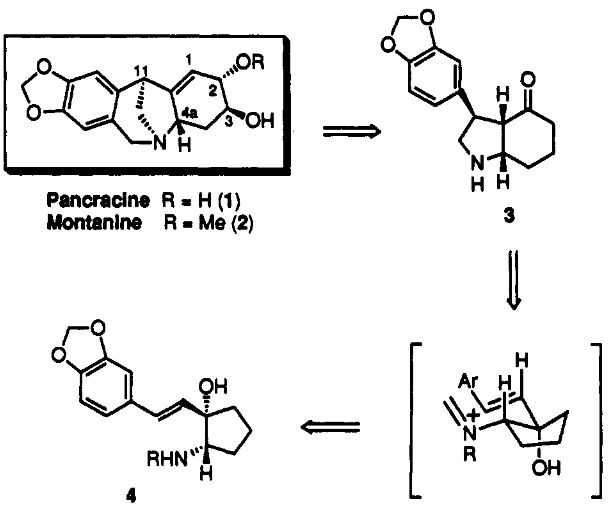
Summary: A tandem aza-Cope rearrangement–Mannich cyclization (**9** → **3**) is the central step in a concise total synthesis of (±)-pancracine.

Over a dozen alkaloids isolated from Amarylidaceae plant species have the unique 5,11-methanomorphanthridine skeleton; pancracine (**1**) and montanine (**2**) are representative examples.[2] Although a massive synthetic effort has been directed toward almost all other types of Amaryllidaceae alkaloids, the methanomorphanthridine group has received scant attention and no total syntheses have been realized.[3] In this paper we reveal a concise route to the methanomorphanthridine subset of Amaryllidaceae alkaloids and specifically describe an efficient and highly stereocontrolled total synthesis of (±)-pancracine (**1**).[4]

The heart of our synthetic plan is outlined in Scheme I and entails establishment of the key C(4a) and C(11) stereorelationship in the aryl *cis*-hydroindolone precursor **3**.[5,6] The well-established chair topography of the aza-Cope–Mannich transformation identifies **4** as the precursor of hydroindolone **3**.[5] The synthesis begins with easily available aminocyclopentanone **5** (Scheme II).[7] Reaction of **5** with the alkynylcerium reagent[8] **6** prepared from 5-ethynyl-1,3-benzodioxole[9] took place with 13:1 facial selectivity, without competing ketone enolization, to afford **7** in 92% yield after purification.[10] Following removal of the cyanomethyl protecting group, propargyl alcohol **8** was reduced with $LiAlH_4$ to provide the crystalline (mp 68–69 °C) *E* allylic alcohol **9**. Reaction of this intermediate at

Scheme I



Pancracine R = H (**1**)
Montanine R = Me (**2**)

3

4

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[1] Synthesis Applications of Cationic Aza-Cope Rearrangements. 23. Part 24: Fevig, J. M.; Overman, L. E.; Marquis, R. W., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 5085.

[2] For comprehensive reviews, see: Martin, S. F. *Alkaloids* (*Academic Press*) **1987**, *30*, 251 and earlier reviews referenced therein.

[3] For synthetic approaches, see: (a) Sánchez, I. H.; Larraza, M. I.; Rojas, I.; Breña, F. K.; Flores, H. J.; Jankowski, K. *Heterocycles* **1985**, *23*, 3033. (b) Hoshino, O.; Ishizaki, M.; Saito, K.; Yumoto, K. *J. Chem. Soc., Chem. Commun.* **1990**, 420.

[4] (a) Wildman, W. C.; Brown, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 6439. (b) Sandberg, F.; Michel, K.-H. *Lloydia* **1963**, *26*, 78. (c) Ali, A. A.; Mesbah, M. K.; Frahm, A. W. *Planta Med.* **1984**, 188.

[5] For a brief review, see: Ricca, D. J.; Overman, L. E. *Comprehensive Organic Synthesis*; Heathcock, C. H., Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford; Vol. 6, in press.

[6] We employ the Wildman[4a] numbering system illustrated in Scheme I.

[7] Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629.

[8] Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

[9] Readily available from piperonal: Feuerstein, W.; Heimann, N. *Chem. Ber.* **1901**, *34*, 1468. Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647.

[10] Yields are for pure compounds purified by chromatography on silica gel and/or recrystallization. Melting points refer to analytical samples typically purified by additional recrystallization.

0022-3263/91/1956-5005$02.50/0