Notes

Pd(0)/Ag$^+$-Cocatalyzed Cyclization Reaction of 1,2-Allenic Carboxylic Acids with Aryl/Alkenyl Halides. An Efficient Synthesis of Butenolides

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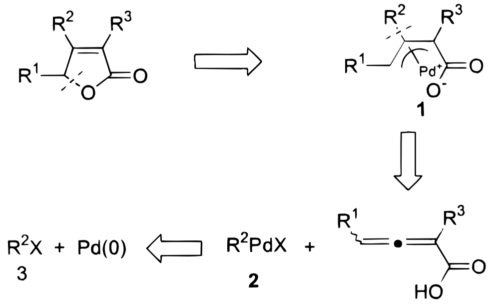
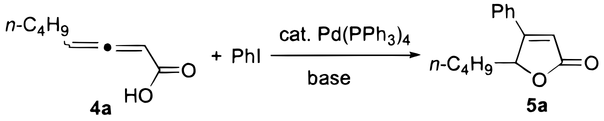
Recently, much attention has been paid to the synthesis of butenolide-containing natural products, which exhibit some interesting biological activities. These compounds were considered as potential insectides, bactericides, fungicides, antibiotics, anticancer agents, antiinflammatories, allergy inhibitors, antipsoriasis agents, cyclooxygenase inhibitors, and phospholipase A$_2$ inhibitors.[1] The butenolide structural unit is usually constructed by one of the following strategies:[2] (1) reaction of metal carbonyl complexes with alkynes;[3] (2) lactonization of 3-hydroxy-1-alkenyl carboxylic acids;[4] (3) selective partial reduction of cyclic anhydrides;[5] (4) regioselective oxidation of substituted furans;[6] (5) Pd-catalyzed carbonylative lactonization of 3-iodo-2(*Z*)-propenol;[7] (6) Pd-catalyzed carbonylative cyclization of 2-alkynols;[8] (7) radical cyclization of 2′-bromoalkyl 2-alkynoates;[9] (8) cyclization of 1,2-allenic carboxylic acids using a variety of electrophiles;[10] (9) Ag$^+$-catalyzed cyclization of 1,2-allenic carboxylic acids.[11] All of these methods have their own scopes, and some of them are either lower-yielding or lengthy. Thus, efficient and general routes to butenolides are still of current interest to synthetic organic chemists.

Scheme 1



Transition-metal-catalyzed methodology has proven to be one of the most powerful pathways for the synthesis of either carbocycles or heterocycles.[12] On the basis of the viewpoint of fundamental reactions in organometallic chemistry, we reasoned that butenolides with different substitution patterns might be generally built up from an oxygen-centered intramolecular nucleophilic substitution of π-allyl palladium intermediate **1**, which, in turn, could be formed via an insertion reaction[13] of the C−Pd bond in carbopalladium intermediate **2** with the C=C bond in 1,2-allenic carboxylic acid (Scheme 1). Due to the easy availability of R^{2}PdX **2** from oxidative addition of R^{2}X with Pd(0), we were interested in developing the Pd-catalyzed *one-step* route from the reaction of organic halides with 1,2-allenylic carboxylic acids to butenolides.



(1)

In 1993, Walkup and co-workers studied the Pd(0)-catalyzed cyclization reaction of aryl halides with 3,4-allenic carboxylic acids.[14] In this reaction, a large excess amount of ArX (5 equiv) was used and the yields were low in most cases. We tested our reaction (eq 1) under this condition; however, the formation of the expected product **5a** was not observed (entry 1, Table 1). The phase-transfer base system K$_2$CO$_3$−*n*-Bu$_4$NCl[15] and Et$_3$N did not work either. Fortunately, when K$_2$CO$_3$ (5 equiv)−EtOH (10 equiv) was used as the base, we observed the formation of **5a**, albeit in lower yield (entry 4, Table 1). When the reaction was carried out in CH$_3$CN with Ag$_2$CO$_3$[16] as the base, **5a** was formed in 53% yield, and only 1.2 equiv of PhI was required (entry 7, Table 1). After further screening, it was found that K$_2$CO$_3$ plus *a*

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(1) Brima, T. S. US Pat. 4,968,817, 1990; *Chem. Abstr.* **1991**, *114*, 185246y. Tanabe, A. Jpn. Kokai Tokkyo. Koho JP. 63,211,276 [88,211,276], 1988; *Chem. Abstr.* **1989**, *110*, 94978q. Lee, G. C. M. Eur. Pat. Appl. EP. 372,940, 1990; *Chem. Abstr.* **1990**, *113*, 191137j. Ducharme, Y.; Gauthier, J. Y.; Prasit, P.; Leblanc, Y.; Wang, Z.; Leger, S.; Therien, M. PCT Int. Appl. WO 95 00,501, 1995; *Chem. Abstr.* **1996**, *124*, 55954y. Lee, G. C. M.; Garst, M. E. PCT Int. Appl. WO 91 16,055, 1991; *Chem. Abstr.* **1992**, *116*, 59197m.

(2) For reviews, see: Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353. Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625.

(3) Deshong, P.; Sidler, D. R. *Tetrahedron Lett.* **1987**, *28*, 2233. Doyama, K.; Joh, T.; Onitsuka, K.; Shiohara, T.; Takahashi, S. *J. Chem. Soc. Chem. Commn.* **1987**, 649.

(4) Tanikaga, R.; Hosoya, K.; Kaji, A. *Synthesis* **1987**, 389.

(5) Urove, G. A.; Welker, M. E. *Organometallics* **1988**, *7*, 1013.

(6) Cottier, L.; Descotes, G.; Nigay, H.; Parron, J.; Grêgoire, V. *Bull. Soc. Chim. Fr.* **1986**, 844. Kernan M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773.

(7) Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238.

(8) Yu, W.; Alper, H. *J. Org. Chem.* **1997**, *62*, 5684. Xiao, W.; Alper, H. *J. Org. Chem.* **1997**, *62*, 3422.

(9) Clough, J. M.; Pattenden, G.; Wight, P. G. *Tetrahedron Lett.* **1989**, *30*, 7469.

(10) Gill, G. B.; Idris, M. S. H. *Tetrahedron Lett.* **1985**, *26*, 4811.

(11) Marshall, J. A.; Wallace, E. M. *J. Org. Chem.* **1995**, *60*, 796.

(12) (a) Ma, S. *Youji Huaxue* **1991**, *11*, 561. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (c) Negishi, E.; Coperet, C.; Ma, S.; Liou, S.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.

(13) For intermolecular carbopalladation of allenes, see: (a) Cazes, B. *Pure Appl. Chem.* **1990**, *62*, 1867, and references therein. (b) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615.

(14) Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88.

(15) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.

(16) For the effect of Ag$_2$CO$_3$ on the intramolecular Heck reaction, see: Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

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Table 1. $Pd(PPh_3)_4$-Catalyzed Cyclization Reaction of PhI with 2,3-Heptadienoic Acid[a]

entry	PhI (equiv)	base (equiv)	solvent	additive (equiv)	temp (°C)/-time (h)	yield[b] of **5a** (%)
1	5	K_2CO_3(5)	DMF		80/7	0
2	5	K_2CO_3(5)	DMF	*n*-Bu_4NCl (0.1)	80/16	0
3	5	Et_3N(3)	CH_3CN		80/16	0
4	5	K_2CO_3(5)	DMF	EtOH (10)	80/16	15[c]
5	2	K_2CO_3(4)	CH_3CN		70/7	29
6	5	K_2CO_3(4)	CH_3CN	EtOH (10)	80/7	49
7	1.2	Ag_2CO_3(1)	CH_3CN		70/7	53
8	1.2	K_2CO_3(4)	CH_3CN	Ag_2CO_3 (1)	70/7	65[c]
9	1.2	K_2CO_3(4)	CH_3CN	Ag_2CO_3 (0.1)	70/7	73[c]
10	1.2	K_2CO_3(4)	CH_3CN	Ag_2CO_3 (0.1)	70/7	47[d]
11	1.2	K_2CO_3(4)	CH_3CN	Ag_2CO_3 (0.1)	40/7	33
12	1.2	K_2CO_3(4)	CH_3CN	Ag_2CO_3 (0.05)	70/7	79[c,e]
13	1.2	K_2CO_3(4)	CH_3CN	$HgCl_2$ (0.05)	70/7	<5
14	1.2	K_2CO_3(4)	CH_3CN	$Hg(OAc)_2$ (0.05)	70/7	<5

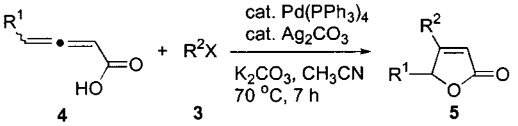
[a] 10% $Pd(PPh_3)_4$ was used, unless otherwise stated. [b] Yield determined by ^1H NMR using CH_2Br_2 as the internal standard. [c] Isolated yield. [d] 2.5% $Pd(PPh_3)_4$ was used. [e] 5% $Pd(PPh_3)_4$ was used.

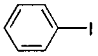
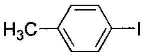
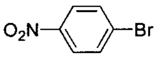
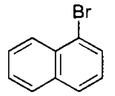
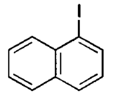
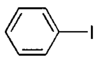
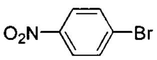
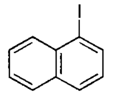
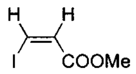
catalytic amount, i.e., 5%, each of $Pd(PPh_3)_4$ and Ag_2CO_3 gave the best results: the reaction was clean, the yield was good, and only 1.2 equiv of PhI was required (compare entries 4–12, Table 1). Although Hg^{2+} was reported to catalyze the cyclization of 1,2-allenic acids,[10] neither $HgCl_2$ nor $Hg(OAc)_2$ could be used in place of Ag_2CO_3 in this reaction (entries 13 and 14, Table 1).

Stimulated by these Pd(0)/Ag^+-cocatalyzed cyclization results, we studied the cyclization of 1,2-allenic carboxylic acids with aryl halides in detail. The results are summarized in Table 2. The reaction of 2,3-dienoic acids with 1-naphthyl iodide afforded **5d** and **5g** in 69% and 72% yields, respectively (entries 5 and 8, Table 2), while 1-naphthyl bromide was inert and did not afford **5d** (entry 4, Table 2). However, for 4-nitrophenyl bromide, the C–Br bond was activated by the *p*-nitro group; thus, the corresponding products **5c** and **5f** were isolated in 64% and 63% yields, respectively (entries 3 and 7, Table 2). The reaction with methyl (*Z*)-3-iodo-2-propenoate[17] also went smoothly under the current reaction conditions (entry 9, Table 2). A coupling constant of 12.6 Hz and a strong NOE correlation observed between the two olefinic protons connected to COOMe in product **5h** confirm that the configuration of the C=C bond remains intact.

On the basis of the results shown in Table 1, it is important to note that the present cyclization reaction might proceed via at least two pathways. In the absence of Ag_2CO_3, the reaction afforded **5a** in lower yield (entries 4–6, Table 1); thus, Ag_2CO_3 must play an important role inside. In addition to the oxidative addition–interomolecular carbopalladation of an allene–intramolecular allylic substitution mechanism (Scheme 2), another plausible mechanism was shown in Scheme 3: a catalytic amount of Ag^+, acting as a Lewis acid,[11,18,19] mediated the formation of the butenolide to form a 3-silver-2-butenolide intermediate,[18,20] which underwent a transmetalation reaction with R^2PdX followed by reductive elimination to afford butenolide **5**. Both Pd(0) and Ag^+ were regenerated after the reaction.

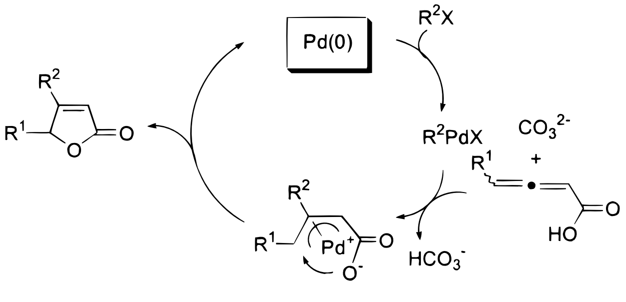
Table 2. $Pd(PPh_3)_4/Ag_2CO_3$-Cocatalyzed Cyclization of Aryl Halides with 1,2-Allenylic Carboxylic Acids[a]



entry	**4** R =	**3**	Isolated yield (%) of **5**
1	*n*-C_4H_9 (**4a**)		79 (**5a**)
2	**4a**		73 (**5b**)
3	**4a**		64 (**5c**)[b]
4	**4a**		0
5	**4a**		69 (**5d**)
6	*n*-C_7H_{15} (**4b**)		77 (**5e**)
7	**4b**		63 (**5f**)[b]
8	**4b**		72 (**5g**)
9	**4a**		59 (**5h**)

[a] **3**/**4**/K_2CO_3/$Pd(PPh_3)_4$/Ag_2CO_3 = 1.2/1/4/0.05/0.05.
[b] 1.5 equiv of *p*-nitrophenyl bromide were used.

Scheme 2



In conclusion, we have developed a new and novel method for the synthesis of butenolides from the easily available aryl/alkenyl halides and 1,2-allenic carboxylic

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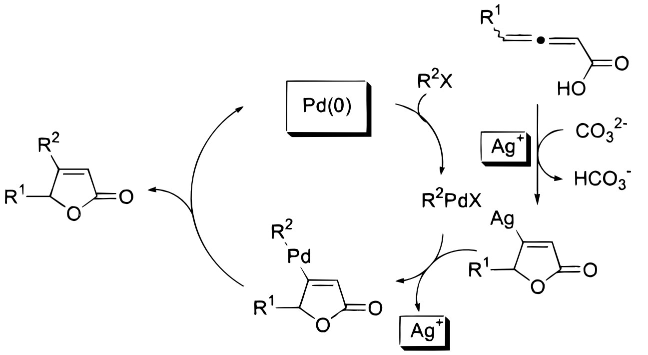
(17) For synthesis of (*Z*)-3-halo-2-propenoic acids and their derivatives, see: Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643. Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709. Lu, X.; Zhu, G.; Ma, S. *Chin. J. Chem.* **1991**, *11*, 267. Ma, S.; Lu, X. *Org. Synth.* **1995**, *72*, 112.

(18) For a recent report on $AgNO_3$-catalyzed synthesis of butenolides from allenic acids, see: Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.

(19) For $AgNO_3$-catalyzed synthesis of 2,5-dihydrofurans from allenylcarbinols, see: (a) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966. Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550.

(20) Westmijze, H.; Ruitenberg, K.; Meijer, J.; Vermeer, P. P. *Tetrahedron Lett.* **1980**, 1771. Meijer, J.; Ruitenberg, K.; Westmijze, H.; Vermeer, P. *Synthesis* **1981**, 551.

Scheme 3



acids.[21] This method should be very general for polysubstituted butenolides. The reaction of differently substituted allenylic carboxylic acids and halides other than aryl/alkenyl halide, such as benylic, allylic, alkynyl halides, as well as investigations regarding the role of Ag^+, and its application in the synthesis of natural and unnatural products of biological importance are being carried out vigorously in our laboratory.

Experimental Section

Starting Materials. 2,3-Heptadienoic acid and 2,3-undecadienoic acid were prepared according to a published procedure[21] via the reaction of CO_2 with corresponding 1,2-allenyllithiums, which, in turn, were prepared from the treatment of the corresponding 1,2-allenes with *n*-BuLi. Phenyl iodide, *p*-nitrophenyl bromide, *p*-methylphenyl iodide, 1-iodonaphthalene, and 1-bromonaphthalene were commerically available and used without further purification. 3-Iodo-2(*Z*)-propenoate[17] was prepared according to the known procedures. ^1H NMR spectra were recorded using $CDCl_3$ as the solvent.

Cyclization Reaction of 1,2-Allenic Carboxylic Acids with Organic Halides. Typical Procedure. (1) Preparation of Compound (5a). To a mixture of 2,3-heptadienoic acid (140 mg, 1.0 mmol), phenyl iodide (245 mg, 1.2 mmol), potassium carbonate (553 mg, 4.0 mmol), and silver carbonate (14 mg, 0.05 mmol) in CH_3CN (3 mL) was added $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) under Ar, and the resulting mixture was heated at 70 °C for 7 h as monitored by TLC. The mixture was then filtered through a short column of silica gel, and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (eluent petroleum ether:ethyl acetate = 10:1) to afford 170 mg of **5a** (79%): liquid; ^1H NMR δ 7.42−7.48 (m, 5H), 6.25 (d, J = 1.4 Hz, 1H), 5.50 (ddd, J = 7.8, 2.8, 1.4 Hz, 1H), 1.95−2.05 (m, 1H), 1.50−1.60 (m, 1H), 1.20−1.46 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H); MS (*m/e*) 216 (M^+), 103 (100); IR (neat) 1735, 1620 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 78.19; H, 7.67.

The following compounds were prepared similarly using the conditions listed in Table 1 and Table 2.

(2) 4-(4′-Methylphenyl)-5-(*n*-butyl)-2(5*H*)-furanone (5b): yield 73%; liquid; ^1H NMR δ 7.38 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 6.26 (s, 1H), 5.45−5.50 (m, 1H), 2.47 (s, 3H), 2.00−2.10 (m, 1H), 1.57−1.64 (m, 1H), 1.18−1.48 (m, 4H), 0.88 (t, J = 6.8 Hz, 3H); MS (*m/e*) 230 (M^+), 145 (100); IR (neat) 1740, 1610 cm^{-1}; HRMS calcd for $C_{15}H_{18}O_2$ 230.1309, found 230.1296.

(3) 4-(4′-Nitrophenyl)-5-(*n*-butyl)-2(5*H*)-furanone (5c): yield, 64%; solid; mp 111−112 °C (*n*-hexane); ^1H NMR δ 8.47 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 6.45 (d, J = 1.2 Hz, 1H), 5.50−5.56 (m, 1H), 1.95−2.01 (m, 1H), 1.55−1.65 (m, 1H), 1.25−1.45 (m, 4H), 0.85 (t, J = 6.80 Hz, 3H); MS (*m/e*) 261 (M^+), 205 (100); IR (KBr) 1725, 1620, 1520, 1340 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.78; N, 5.36. Found: C, 64.07; H, 5.70; N, 5.16.

(4) 4-(1′-Naphthyl)-5-(*n*-butyl)-2(5*H*)-furanone (5d): yield, 69%; liquid; ^1H NMR δ 8.02−8.08 (m, 1H), 7.85−7.95 (m, 2H), 7.53−7.65 (m, 2H), 7.50 (d, J = 7.2 Hz, 1H), 7.40 (d, J = 7.2 Hz, 1H), 6.35 (d, J = 1.5 Hz, 1H), 5.54 (ddd, J = 7.9, 3.2 and 1.5 Hz, 1H), 1.72−1.82 (m, 1H), 1.45−1.55 (m, 1H), 1.35−1.45 (m, 2H), 1.18−1.30 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H); MS (*m/e*) 266 (M^+), 152 (100); IR (neat) 1740, 1620 cm^{-1}; HRMS calcd for $C_{18}H_{18}O_2$ 266.0958, found 266.1309.

(5) 4-Phenyl-5-(*n*-heptyl)-2(5*H*)-furanone (5e): yield, 77%; liquid; ^1H NMR δ 7.40−7.50 (m, 5H), 6.28 (d, J = 1.4 Hz, 1H), 5.49 (ddd, J = 7.6, 2.7, 1.4 Hz, 1H), 1.95−2.03 (m, 1H), 1.46−1.62 (m, 1H), 1.10−1.35 (m, 10H), 0.82 (t, J = 7.2 Hz, 3H); MS (*m/e*) 259 ($M^+ + 1$, 100), 258 (M^+); IR (neat) 1735, 1615 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.53. Found: C, 78.66; H, 8.52.

(6) 4-(4′-Nitrophenyl)-5-(*n*-heptyl)-2(5*H*)-furanone (5f): yield, 63%; solid; mp 144−6 °C (*n*-hexane); ^1H NMR δ 8.36 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 6.45 (d, J = 1.2 Hz, 1H), 5.50−5.56 (m, 1H), 1.95−2.01(m, 1H), 1.55−1.80 (m, 1H), 1.10−1.45 (m, 10H), 0.85 (t, J = 6.1 Hz, 3H); MS (*m/e*) 303 (M^+), 218 (100); IR (KBr) 1740, 1620, 1520, 1340 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.08; H, 6.93; N, 4.68.

(7) 4-(1′-Naphthyl)-5-(*n*-heptyl)-2(5*H*)-furanone (5 g): yield, 72%; liquid; ^1H NMR δ 7.95−8.02 (m, 1H), 7.85−7.95 (m, 2H), 7.50−7.60 (m, 2H),7.46 (d, J = 7.1 Hz, 1H), 7.34 (d, J = 7.1 Hz, 1H), 6.34 (d, J = 1.5 Hz, 1H), 5.62 (ddd, J = 7.9, 3.2, 1.5 Hz, 1H), 1.72−1.82 (m, 1H), 1.45−1.65 (m, 1H), 1.36−1.45 (m, 2H), 1.05−1.35 (m, 8H), 0.82 (t, J = 7.2 Hz, 3H); MS (*m/e*) 308 (M^+), 152 (100); IR (neat) 1740, 1615 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.60; H, 8.00.

(8) (*Z*)-4-(2′-Methoxycarbonylvinyl)-5-(*n*-butyl)-2(5*H*)-furanone (5h): yield, 59%; liquid; ^1H NMR δ 6.55 (d, J = 12.6 Hz, 1H), 6.38 (s, 1H), 6.15 (d, J = 12.6 Hz, 1H), 5.38−5.44 (m, 1H), 3.73 (s, 3H), 1.85−1.90 (m, 1H), 1.20−1.45 (m, 5H), 0.90 (t, J = 6.9 Hz, 3H); MS (*m/e*) 224 (M^+), 57 (100); IR (neat) 1750, 1725, 1200 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.60; H, 6.98.

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Supporting Information Available: The ^1H NMR spectra of the compounds **5a**, **5b**, and **5d** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[21] Venkruijsse, H. D.; Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes. A Laboratory Manual*; Elsevier: Amsterdam, The Netherlands, 1981; p 33.