Facile One-Pot Preparation of Functionalized 2-Vinylidenehydrofurans by Tandem *C*−*O*-Cycloalkylation of Stabilized Carbanions

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Functionalized allenes are well represented in biologically active molecules and constitute powerful C-3 units with a wide range of synthetic applications.[1] Among them, the preparation and the chemistry of acyclic alkoxyallenes have received particular interest, and elegant exploitations in heterocyclization, cycloaddition, spiroannulation, and cyclopentannulation reactions were reported.[2] However, quite surprisingly the cyclic version, namely, the synthesis of stable and synthetically valuable vinylidenehydrofurans, still represents, to the best of our knowledge, a challenging problem.[3] Indeed, while very recently a new synthetic route to hitherto unknown 3-vinylidenetetrahydrofurans was reported,[4] 2-substituted analogues are only involved as highly reactive intermediates in the powerful Marshall's synthesis of furans.[5]

In this paper we describe the first preparation of stable 2-vinylidenehydrofurans **8**−**12** by using our recently reported one-pot tandem *C*−*O*-cycloalkylation procedure.[6] The sequence is illustrated in Scheme 1. Easily accessible alkanones **1**−**5** react smoothly, in refluxing THF in the presence of an excess of K_2CO_3, with 1,4-dibromobut-2-yne (**6**).[7]

A simple filtration through a short pad of Celite furnishes good yields of allenyl enol ethers **8**−**12** with generally very high chemical purity (Table 1). For stereoelectronic reasons,[8] an intramolecular *C*-Michael addition to the activated triple bond in intermediate **7** is forbidden allowing a clean S_N2' *O*-displacement leading to the corresponding heterocycles. Our heterocyclization proved to be quite general and allows the facile construction of previously unknown fused polycyclic and monocyclic heterocycles of high synthetic value.

An example of the reactivity and the synthetic potentiality of these new 2-vinylidenehydrofurans[9] is presented by the facile isomerization, upon purification on silica gel, of **12** to the corresponding 2,3,5-trisubstituted vinylfuran **13**. Interestingly this heterocyclic nucleus represents an important substructure of numerous marine cembranolides[10] and offers a variety of synthetically

Scheme 1

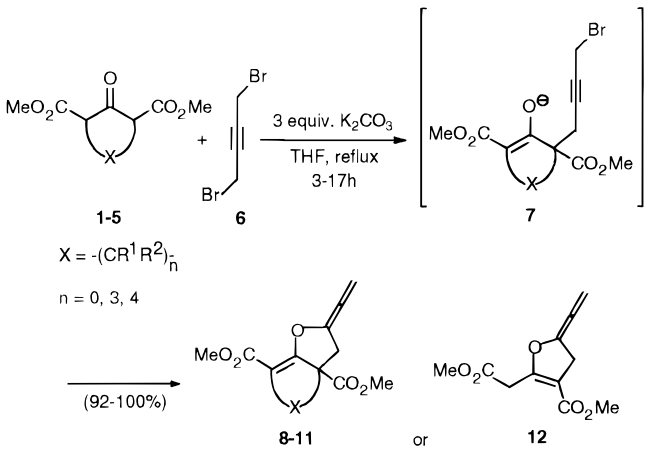
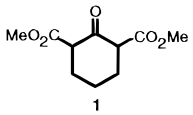
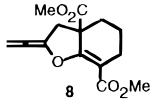
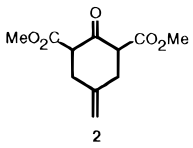
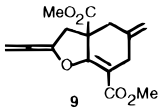
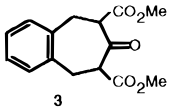
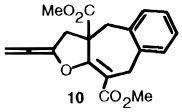
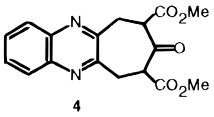
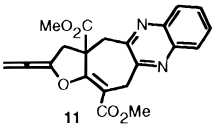
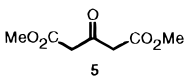
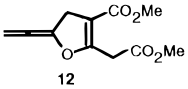


Table 1. One-Pot Synthesis of Allenyl Enol Ethers

Substrate	t, h	Product	Yield, %
 1	17	 8	92
 2	8	 9	94
 3	3	 10	93
 4	3	 11	100
 5	4	 12	95[a]

[a] Crude, >95% pure by ^{1}H NMR.

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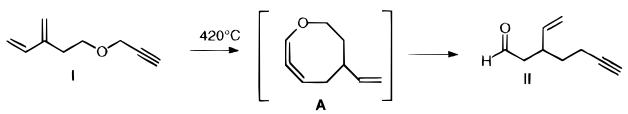
(1) *The Chemistry of the Allenes*; Landor, S. R., Ed.; Academic Press: London, 1982. Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984.

(2) Zimmer, R. *Synthesis* **1993**, 165.

(3) Computer-assisted structural search on REACS database gave only one answer concerning the transient existence of structurally related oxocycloocta-2,3-diene **A**, intermediate during the thermal rearrangement of dienyne ether **I** to aldehyde **II**; see: Shea, K. J.; Burke, L. D.; England, W. P. *Tetrahedron Lett.* **1988**, *29*, 407. See also: Hopf, H. In *The Chemistry Of Ketenes, Allenes and Related Compounds*, part 2; Patai, S., Ed.; J. Wiley and Sons Ltd.: New York, 1980, p 842. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapters 1.1, 1.2, 1.8, and 1.9.



(4) Dulcère, J. P.; Dumez, E.; Faure, R. *J. Chem. Soc., Chem. Commun.* **1995**, 897.

(5) Marshall, J. A.; Dubay, W. J. *J. Org. Chem.* **1993**, *58*, 3435; **1994**, *59*, 1703.

(6) Lavoisier, T.; Rodriguez, J. *Synlett* **1996**, 339.

(7) Johnson, A. W. *J. Chem. Soc.* **1946**, 1009. For a recent review on the use of functionalized alkynes, see: Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.

(8) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977**, 233. Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939.

(9) For recent examples of the preparation and the chemistry of related 2-methylenetetrahydrofurans, see: Dalla, V.; Pale, P. *Tetrahedron Lett.* **1996**, *37*, 2777, 2781. Edwards, G. L.; Muldoon, C. A.; Sinclair, D. J. *Tetrahedron* **1996**, *52*, 7779.

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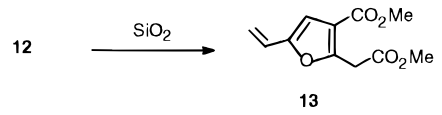
Scheme 2



exploitable functionalities such as two diene units and two chemically differentiated ester functions.

Further studies aimed at the development of the promising chemistry offered by this new class of heterocycles are under active investigation.

Experimental Section

General. Dimethyl 1,3-acetonedicarboxylate (**5**) was purchased from Aldrich. Cyclohexanones **1** and **2** were prepared by minor modification of a literature procedure,[11] while ketones **3** and **4** were obtained in good yields by α,α'-dialkylation of **5** with the required 1,4-dihalides.[7] Dry THF distilled from Na/benzophenone ketyl was used in all condensations. IR spectra were recorded neat or in $CHCl_3$, and NMR spectra were obtained at 200 MHz in $CDCl_3$ using residual $CHCl_3$ as internal reference; *J* values are given in hertz (Hz).

General Procedure for the Preparation of Allenyl Enol Ethers. To a solution of keto dicarboxylate (1 mmol) in dry THF (15 mL) was added powdered K_2CO_3 (2.5 mmol), and the mixture was stirred under nitrogen for 15 min at room temperature. 1,4-Dibromobut-2-yne (**6**) (1.1 mmol) in dry THF (10 mL) was than added *via* a syringe, and the resulting reaction mixture was stirred under reflux for the indicated time (Table 1). After completion, filtration through a short pad of Celite and evaporation of the THF under reduced pressure gave crude allenyl enol ethers with very high chemical purity. Analytical samples were obtained by rapid flash chromatography on Et_3N-deactivated SiO_2 except in the case of **12** which suffered partial isomerization to **13** (see Scheme 2).

2-Vinylidene-2,3,5,6-tetrahydro-4*H*-benzofuran-3a,7-dicarboxylic acid dimethyl ester (8): $R_f = 0.53$ (diethyl ether−pentane, 7/3); IR (neat) ν/cm^{-1} 2953, 1990, 1666, 1437, 1118, 914; ^{1}H NMR δ 1.39−1.56 (m, 2H), 1.81−1.96 (m, 1H), 2.35−2.42 (m, 2H), 2.43−2.59 (m, 1H), 2.73 (dt, J = 15.0, 5.7, 1H), 3.10 (dt, J = 14.9, 1.6, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 5.54 (dt, J = 5.7, 1.6, 2H); ^{13}C NMR δ 19.4, 23.7, 31.5, 37.9, 51.6, 53.0, 53.4, 92.6, 102.5, 129.0, 160.7, 166.8, 173.0, 195.3.

5-Methylene-2-vinylidene-2,3,5,6-tetrahydro-4*H*-benzofuran-3a,7-dicarboxylic acid dimethyl ester (9): $R_f = 0.51$ (diethyl ether−pentane, 7/3); IR (neat) ν/cm^{-1} 2953, 1986, 1732, 1696, 1669, 1437, 1148, 732; ^{1}H NMR δ 2.23 (d, J = 12.4, 2H), 2.81 (dt, J = 15.1, 5.8, 1H), 3.00−3.30 (m, 3H), 3.66 (s, 3H), 3.76 (s, 3H), 4.87 (m, 1H), 4.96 (m, 1H), 5.52−5.57 (dm, J = 4.8, 2H); ^{13}C NMR δ 31.1, 36.9, 40.5, 51.3, 52.5, 54.9, 92.5, 101.1, 112.8, 129.2, 138.9, 160.8, 165.8, 171.6, 194.9. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.96; H, 5.78.

2-Vinylidene-2,3,4,9-tetrahydro-1-oxabenz[*f*]azulene-3a,10-dicarboxylic acid dimethyl ester (10): $R_f = 0.64$ (diethyl ether−pentane, 7/3); IR (neat) ν/cm^{-1} 2952, 1985, 1736, 1652, 1435, 1199, 1147, 911; ^{1}H NMR δ 2.89 (dt, J = 14.7, 5.7, 1H), 3.09−3.42 (m, 1H), 3.17 (d, J = 14.0, 1H), 3.34 (d, J = 14.0, 1H), 3.46 (s, 3H), 3.48−3.76 (m, 2H), 3.78 (s, 3H), 5.48−5.57 (m, 2H), 7.04−7.22 (m, 4H); ^{13}C NMR δ 31.5, 37.2, 38.4, 51.7, 52.7, 56.3, 92.5, 106.0, 126.6, 127.2, 127.8, 129.0, 129.4, 134.7, 139.9, 160.1, 167.2, 172.0, 194.9.

2-Vinylidene-2,3,4,11-tetrahydro-1-oxa-5,10-diazanaphth-[2,3-*f*]azulene-3a,12-dicarboxylic acid dimethyl ester (11): white crystals, mp 145−147 °C; $R_f = 0.44$ (diethyl ether); IR ($CHCl_3$) ν/cm^{-1} 2953, 1986, 1738, 1694, 1650, 1436, 1317, 1151, 910; ^{1}H NMR δ 3.01 (dt, J = 15.1, 5.3, 1H), 3.41−3.56 (m, 1H), 3.54 (d, J = 15.3, 1H), 3.62 (s, 3H), 3.79 (s, 3H), 3.89 (d, J = 15.3, 1H), 4.05 (d, J = 16.4, 1H), 4.27 (d, J = 16.4, 1H), 5.48−5.64 (m, 2H), 7.65−7.74 (m, 2H), 7.95−8.06 (m, 2H); ^{13}C NMR δ 33.8, 37.5, 41.2, 52.1, 53.5, 55.2, 93.3, 103.7, 128.3, 128.8, 128.9, 129.4, 129.7, 140.9, 141.2, 151.3, 154.2, 161.2, 166.1, 171.3, 194.9. Anal. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.59; H, 4.78; N, 7.28.

2-[(Methoxycarbonyl)methyl]-5-vinylidene-4,5-dihydrofuran-3-carboxylic acid methyl ester (12): $R_f = 0.55$ (diethyl ether−pentane, 7/3); IR (neat) ν/cm^{-1} 2955, 2067, 1980, 1744, 1710, 1660, 1441, 1115, 1044, 756; ^{1}H NMR δ 3.66−3.84 (m, 2H), 3.70 (s, 3H), 3.71 (s, 3H), 3.78 (s, 2H), 5.54 (t, J = 6.4, 2H); ^{13}C NMR δ 31.9, 33.3, 51.2, 52.3, 92.5, 106.4, 131.2, 160.8, 164.4, 167.9, 196.2.

2-[(Methoxycarbonyl)methyl]-5-vinylfuran-3-carboxylic acid methyl ester (13): $R_f = 0.55$ (diethyl ether−pentane, 7/3); IR (neat) ν/cm^{-1} 2960, 1747, 1721, 1439, 1412, 1260, 1076, 788; ^{1}H NMR δ 3.71 (s, 3H), 3.80 (s, 3H), 4.05 (s, 2H), 5.21 (dd, J = 11.3, 1.0, 1H), 5.67 (dd, J = 17.5, 1.0, 1H), 6.41 (dd, J = 17.5, 11.3, 1H), 6.51 (s, 1H); ^{13}C NMR δ 33.7, 51.6, 52.5, 108.2, 114.1, 116.9, 124.3, 152.4, 153.5, 163.8, 169.1. Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 56.02; H, 5.37.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra with complete characterization for compounds **8**−**13** (13 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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(10) Rodriguez, A. D.; Soto, J. J. *Tetrahedron Lett.* **1996**, *37*, 2687 and references cited therein.

(11) Blike, F. F.; McCarty, F. J. *J. Org. Chem.* **1959**, *24*, 1069.