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Facile Strategy to 3-Acylfurans by Silver(I)/Celite-Mediated Cycloaddition of 1,3-Dicarbonyl Compounds to Vinyl Sulfides. First Total Synthesis of α-Clausenan

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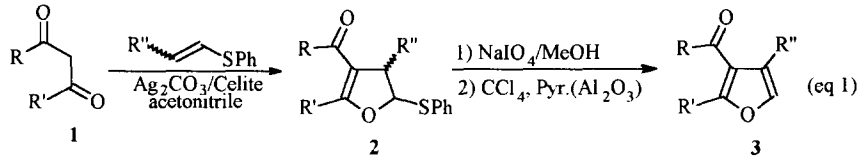
Abstract: *An efficient synthesis of 3-acylfurans is achieved by silver(I)/Celite- mediated cycloaddition of dicarbonyl compounds with vinyl sulfides.* © 1997 Elsevier Science Ltd.

Furans are one of the most important heteroaromatic compounds with widespread occurrence in nature.[1] They are frequently found in many natural products arising from plants and marine organisms.[2] Possessing a variety of biological activities, they are used as pharmaceutical agents, for flavor, fish antifeedant agents and as insecticides.[3] Their important biological activities and usefulness as synthetic intermediates of natural products have prompted a search for better methods of synthesis. Although a number of synthetic methods for the preparation of 3-acylfurans have been reported, simple and efficient approaches still remain scarce.[4]

Oxidative radical reactions mediated by metal salts (Mn(III), Ce(IV), and Co(II)) have become an important method for the synthesis of heterocyclic frameworks.[5] We have been interested in oxidative radical cycloaddition of 1,3-dicarbonyl compounds to alkenes. In a previous communication, we have reported that silver(I)/Celite is a simple and convenient reagent for dihydrofuran formation.[6] We describe here the efficient synthesis of 3-acylfurans by the oxidative cycloaddition of 1,3-dicarbonyl compounds to vinyl sulfides followed by $NaIO_4$ oxidation and *syn*-elimination under mild conditions (eq. 1).

The sequence that we have developed begins with the reaction of 1,3-dicarbonyl compounds with vinyl sulfides (3-fold excess) in acetonitrile. Two equivalents of Ag_2CO_3/Celite are used for the formation of the dihydrofuran. The course of the reaction can be readily monitored by TLC. Isolation of products involves a very simple filtration to remove the reduced silver metal followed by evaporation of the solvent.

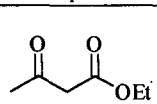
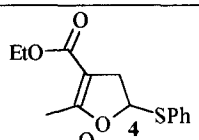
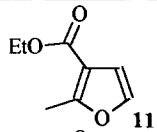
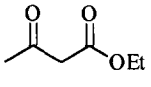
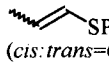
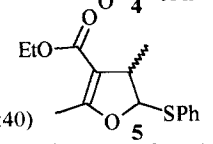
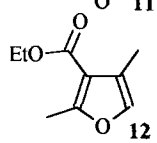
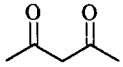
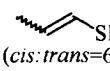
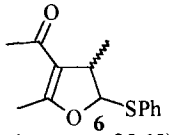
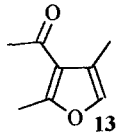
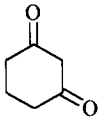
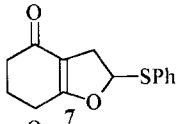
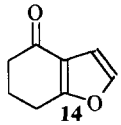
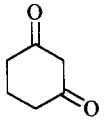
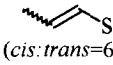
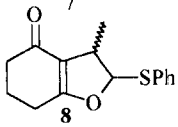
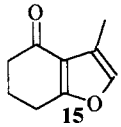
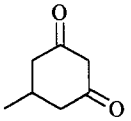
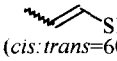
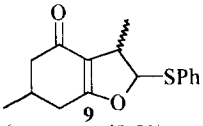
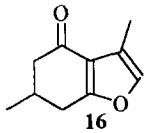
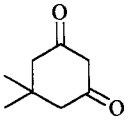
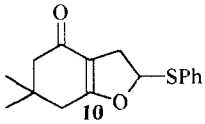
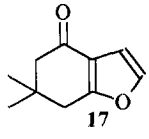


1 2 3

The formation of the dihydrofuran is confirmed by analysis of the expected chemical shifts and geminal coupling constants associated with the methylene group of the dihydrofuran ring.[7] The stereochemical assignment of *cis*- and *trans*-isomers was defined by comparison of the coupling constants between vicinal protons. The results are summarized in Table 1.

Next, the intermediate dihydrofurans were treated with sodium periodate in aqueous methanol at room temperature for 24 h to form the corresponding sulfoxide, which on refluxing for 2 h with pyridine in carbon tetrachloride directly delivers the 3-acylfurans in high yield (eq. 1). The structure of the 3-acylfurans is easily identified by the chemical shift of the vinylic proton in the furan ring.[8] Both stereoisomers of *cis* and *trans* were also similarly transformed into 3-acyl-4-methylfuran in good yield;

Table 1. Synthesis of Dihydrofurans and Furans

entry	1,3-dicarbonyl compound	vinyl sulfide	dihydrofuran	furan	yield	
					dihydrofuran	furan
1			 **4**	 **11**	49	82
2		 (*cis*:*trans*=60:40)	 **5** (*cis*:*trans*=30:70)	 **12**	63	78
3		 (*cis*:*trans*=60:40)	 **6** (*cis*:*trans*=35:65)	 **13**	83	50
4			 **7**	 **14**	77	79
5		 (*cis*:*trans*=60:40)	 **8** (*cis*:*trans*=46:54)	 **15**	79	65
6		 (*cis*:*trans*=60:40)	 **9** (*cis*:*trans*=49:51)	 **16**	86	77
7			 **10**	 **17**	77	91

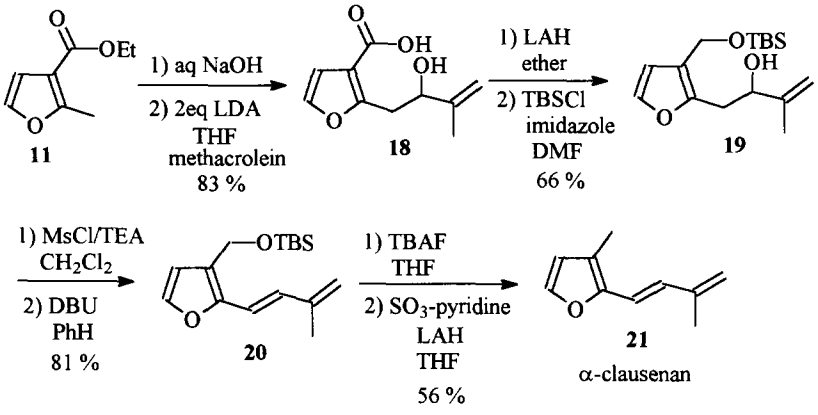
although, active alumina had to be added in the elimination step to cause epimerization of the *cis*-sulfoxide prior to *syn*-elimination of the sulphenic acid. These transformations had been reported by Yoshikoshi in a 3-methylfuran annulation from 1,3-dicarbonyl compounds by using a phenylthionitroolefin.[9] The data of the 3-acylfurans are also shown in Table 1.

The synthesis of evodone **16**, a furanomonoterpene isolated from *Evonia hortensis* Forst,[10] demonstrates an interesting application of this methodology. The spectroscopic properties of our synthetic evodone agreed well with those reported in the literature.

Another application of this technology to the total synthesis of a furanoterpene, α-clausenan **21**, was next examined. α-Clausenan **21** has been isolated with rosefuran as a mixture from leaves of *Clausena*

willdenovii , a large of shrub found in the Himalayas, Sri Lanka, and some elevated parts of southern and western India.[11] The structure of α-clausenan was established by spectroscopic analysis, but no synthetic methods are known.

The conversion of compound **11** to natural product α-clausenan was begun by hydrolysis with aq. NaOH (Scheme 1). This was followed by alkylation of the dianion generated from furoic acid and two equivalents of lithium diisopropylamide,[12] to give compound **18** in 83% yield (2 steps). Reduction of the acid **18** with lithium aluminum hydride in ether and protection of the resulting diol with one equivalent of t-butyldimethylsilyl (TBS) chloride as a standard condition afforded the desired secondary alcohol **19** (66%, 2 steps). Construction of a butadienyl group was accomplished in good yield by mesylation of the alcohol **19** with methanesulfonyl chloride followed by elimination of the corresponding mesylate with DBU (81%, 2 steps). The TBS group of **20** was removed with TBAF in THF to produce the corresponding allylic alcohol, which was easily reduced with SO_3-pyridine and LAH[13] to give the natural product α-clausenan, **21**(56 %, 2 steps). Spectral data[14] and a physical property[15] of our synthetic product are in agreement with those reported in the literature.



Scheme 1

In conclusion, a highly efficient method for constructing fused 3-acylfurans from 1,3-dicarbonyl compounds with vinyl sulfides is described. The application of this methodology to the synthesis of evodone **16** and α-clausenan **21** is also reported. Further application of this furan annulation is expected in the synthesis of a variety of furanoterpenoids and now is in progress in our laboratory.

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5. Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
6. Lee, Y. R.; Kim, B. S. *Tetrahedron Lett.* **1997**, *38*, 2095.
7. Spectral data for **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.28 (5H, m), 5.95 (1H, dd, J=10.0, 5.9 Hz), 4.16 (2H, q, J=7.1 Hz), 3.34 (1H, dd, J=15.8, 10.0 Hz), 2.86 (1H, dd, J=15.8, 5.8 Hz), 2.21 (3H, s), 1.27 (3H, t, J=7.1 Hz); IR (neat) 3059, 2980, 1699, 1653, 1479, 1440, 1383, 1084, 954, 898, 742 cm^{-1}. **5**: *cis*-isomer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.28 (5H, m), 5.92 (1H, d, J=8.6 Hz), 4.18 (2H, m), 3.48 (1H, m), 2.23 (3H, s), 1.30 (6H). *trans*-isomer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.28 (5H, m), 5.42 (1H, d, J=4.6 Hz), 4.18 (2H, m), 3.17 (1H, m), 2.22 (3H, s), 1.30 (6H); IR (neat) 3059, 2980, 1699, 1651, 1583, 1479, 1440, 1381, 1340, 1082, 771, 742 cm^{-1}. **6**: *cis*-isomer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.29 (5H, m), 5.88 (1H, d, J=8.4 Hz), 3.51 (1H, m), 2.28 (3H, s), 2.27 (3H, s), 1.30 (3H, d, J=6.9 Hz). *trans*-isomer ^{1}H NMR (300MHz, $CDCl_3$) δ 7.51-7.30 (5H, m), 5.43 (1H, d, J=3.9 Hz), 3.23 (1H, m), 2.22 (3H, s), 2.24 (3H, s), 1.27 (3H, d, J=6.8 Hz); IR (neat) 3059, 1672, 1626, 1481, 1440, 1386, 1211, 1147, 1024, 949, 779, 744 cm^{-1}. **7**: mp. 73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.33 (5H, m), 6.09 (1H, dd, J=9.7, 6.1 Hz), 3.25 (1H, dd, J=15.3, 10.1 Hz), 2.83 (1H, dd, J=15.7, 5.6 Hz), 2.45 (2H, m), 2.32 (2H, m), 2.02 (2H, m); IR (KBr) 2943, 1640, 1481, 1440, 1394, 1222, 1178, 1058, 1021, 900, 870, 839 cm^{-1}. **8**: *cis*-isomer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.30 (5H, m), 6.10 (1H, d, J=8.9 Hz), 3.58 (1H, m), 2.44 (2H, m), 2.30 (2H, m), 2.03 (2H, m), 1.37 (3H, d, J=7.0 Hz). *trans*-isomer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.30 (5H, m), 5.54 (1H, d, J=5.4 Hz), 3.20 (1H, m), 2.44 (2H, m), 2.30 (2H, m), 2.03 (2H, m), 1.31 (3H, d, J=6.8 Hz); IR (neat) 3057, 2947, 1639, 1583, 1481, 1396, 1222, 1180, 902, 875, 742 cm^{-1}. **9**: *cis*-isomer ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.30 (5H, m), 6.10 (1H, d, J=9.0 Hz), 3.57 (1H, m), 2.53-2.11 (5H, m), 1.36 (3H, d, J=7.0 Hz), 1.10 (3H, d, J=5.9 Hz); IR (neat) 2953, 1642, 1439, 1395, 1204, 1138, 1023, 911, 881, 742 cm^{-1}. *trans*-isomer ^{1}H NMR 300 MHz, $CDCl_3$) δ 7.53-7.30 (5H, m), 5.55 (1H, d, J=5.6 Hz), 3.20 (1H, m), 2.53-2.04 (5H, m), 1.31 (3H, d, J=6.8 Hz), 1.10 (3H, d, J=6.2 Hz); IR (neat) 2945, 1641, 1397, 1205, 1022, 890, 742 cm^{-1}. **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.31 (5H, m), 6.15 (1H, dd, J=9.9, 6.1 Hz), 3.33 (1H, dd, J=15.7, 9.9 Hz), 2.88 (1H, dd, J=15.7, 6.1 Hz), 2.34 (2H, d, J=2.0 Hz), 2.24 (2H, s), 1.13 (3H, s) 1.12 (3H, s); IR (neat) 3057, 2959, 1641, 1583, 1400, 1255, 1167, 1143, 1095, 912, 877 cm^{-1}.
8. Spectral data for **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (1H, d, J=2.0 Hz), 6.23 (1H, d, J=1.9 Hz), 4.28 (2H, q, J=7.1 Hz), 2.56 (3H, s), 1.34 (3H, t, J=7.1 Hz); IR (neat) 3130, 2984, 1716, 1606, 1521, 1429, 1300, 1234, 1134, 1097, 947, 736 cm^{-1}. **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (1H, s), 4.28 (2H, q, J=7.1 Hz), 2.53 (3H, s), 2.13 (3H, d, J=1.2 Hz), 1.35 (3H, t, J=7.1 Hz); IR (neat) 2980, 1714, 1612, 1562, 1417, 1273, 1099 cm^{-1}. **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (1H, s), 2.55 (3H, s), 2.43 (3H, s), 2.17 (3H, s); IR (neat) 2964, 1668, 1593, 1396, 1271, 1070, 943 cm^{-1}. **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (1H, d, J=2.0 Hz), 6.67 (1H, d, J=2.0 Hz), 2.89 (2H, m), 2.50 (2H, m), 2.50 (2H, m), 2.18 (2H, m); IR (neat) 3131, 2948, 1677, 1595, 1516, 1447, 1414, 1294, 1242, 1184, 1189, 1026 cm^{-1}. **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (1H, s), 2.83 (2H, t, J=6.3 Hz), 2.47 (2H, t, J=6.0 Hz), 2.19 (3H, s), 2.14 (2H, m); IR (neat) 2953, 1672, 1560, 1433, 1180, 1145, 1076 cm^{-1}. **16**: mp. 70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (1H, s), 2.92-2.11 (5H, m), 2.18 (3H, s), 1.14 (3H, d, J=6.3 Hz); IR (KBr) 3000, 2966, 1662, 1603, 1560, 1456, 1440, 1430, 1390, 1324, 1242, 1139, 1080, 1045, 1001 cm^{-1}. **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (1H, d, J=1.9 Hz), 6.67 (1H, d, J=1.9 Hz), 2.76 (2H, s), 2.39 (2H, s), 1.15 (6H, s); IR (neat) 3132, 2952, 2878, 1678, 1596, 1514, 1445, 1370, 1281, 1228, 1174, 1118, 1042 cm^{-1}.
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14. Spectral data for **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (1H, d, J=2.0 Hz), 6.64 (1H, d, J=2.0 Hz), 4.93 (1H, s), 4.79 (1H, s), 4.39 (1H, t, J=6.3 Hz), 3.21 (2H, m), 1.75 (3H, s); IR (neat) 3410, 2924, 1687, 1601, 1520, 1454, 1307, 1242, 1026, 898, 742 cm^{-1}. **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (1H, d, J=1.8 Hz), 6.29 (1H, d, J=1.8 Hz), 4.99 (1H, s), 4.84 (1H, s), 4.52 (2H, s), 4.26 (1H, m), 2.90 (2H, m), 1.77 (3H, s), 0.91 (9H, s), 0.11 (6H, s); IR (neat) 3362, 2955, 1651, 1624, 1512, 1469, 1255, 1072, 837, 775 cm^{-1}. **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, d, J=1.8 Hz), 6.80 (1H, d, J=16.0 Hz), 6.41 (1H, d, J=15.9 Hz), 6.39 (1H, d, J=1.8 Hz), 5.11 (1H, s), 5.05 (1H, s), 4.63 (2H, s), 1.93 (3H, s), 0.92 (9H, s), 0.09 (6H, s); IR (neat) 2955, 2858, 1614, 1471, 1377, 1255, 1097, 1068, 839, 777 cm^{-1}. **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (1H, d, J=1.6 Hz), 6.76 (1H, d, J=16.0 Hz), 6,33 (1H, d, J=16.0 Hz), 6.24 (1H, d, J=1.6 Hz), 5.09 (1H, s), 5.02 (1H, s), 2.09 (3H, s), 1.95 (3H, s); IR (neat) 2974, 1612, 1572, 1494, 1452, 1379, 1259, 1087, 954, 891 cm^{-1}.
15. This synthetic material exhibited a very labile nature and a tendency to resinify in air as reported by Subba Rao.

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