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A Facile Synthesis of Dihydrofurans Utilizing Silver(I)/Celite Promoted Oxidative Cycloaddition of 1,3-Dicarbonyl Compounds to Alkenes

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Abstract: *An efficient synthesis of dihydrofurans has been carried out starting from 1,3-dicarbonyl compounds* © 1997 Elsevier Science Ltd.

The oxidative addition reaction of carbon-centered radicals to alkenes mediated by metal salts (Mn^{III}, Ce^{IV}, and Co^{II}) has received considerable attention over the last decade in organic synthesis for construction of carbon-carbon bonds.[1] The utilization of high valent metal salts in oxidative addition reactions has been particularly effective. Among these, manganese(III) acetate and cerium(IV) ammonium nitrate (CAN) have been used most efficiently.[2-3] However, their synthetic exploitation has been limited by strong acidic reaction conditions and by overoxidations due to substitution of acetate or nitroxy groups.[4-6] Necessity for overcoming these problems has prompted our search for the possibility of using silver(I) metals. In related work, Malek[7] has demonstrated the usefulness of Ag(II) oxide for the generation of a carbon radical and Saegusa[8] has reported the oxidative dimerization of β-diketone by using Ag(I) oxide. It has been also reported by Fetizon that silver(I) carbonate/Celite is a valuable reagent for the oxidation of alcohols to aldehydes and ketones in high yield.[9]

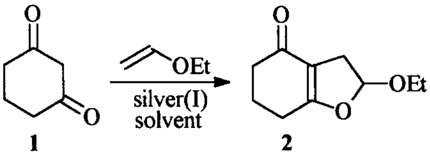
Precedents for a process in which Mn(III) and Ce(IV) mediated oxidative additions of 1,3-dicarbonyl compounds to olefins deliver the dihydrofurans come from the work of Corey[10] and Baciocchi.[11] We have been interested in transition metal mediated oxidative radical cyclization of 1,3-dicarbonyl compounds with olefins. We report here that Ag(I)/Celite is an efficient and useful reagent for the oxidative cycloaddition of 1,3-dicarbonyl compounds to olefins, which allows the synthesis of dihydrofurans in good yield.

Two equivalents of Ag(I)/Celite are used to bring the reaction to completion. The reactions are typically carried out by refluxing a solution of a 1,3-dicarbonyl compound with an alkene (5 eq) in an anhydrous solvent. Reaction of 1,3-cyclohexanedione **1** with ethyl vinyl ether was attempted utilizing several silver(I) reagents. Both silver(I) oxide and silver(I) carbonate provided the desired dihydrofuran **2** in good yields, whereas AgOAc, $AgNO_3$, and $AgBF_4$ gave no reaction. Most interestingly, we found that the readily available reagents, 50% silver(I) oxide/Celite or 50% silver(I) carbonate/Celite, are more efficient than silver(I) oxide or silver(I) carbonate for the production of dihydrofuran **2** as shown in Table 1. More importantly, the incorporation of Celite resulted in reduced reaction time and in improved yields. However, addition of silica gel resulted in a low yield (31%).

In an effort to optimize reaction conditions, we surveyed several solvents for the production of dihydrofuran **2** with the Ag_2O/Celite system (Table 1). Nonpolar solvents such as benzene or heptane gave only low yields (15% or 10%) of dihydrofuran **2**, presumably due to the insolubility of silver(I) oxide. In contrast, when the polar solvent acetonitrile was used, the yield was dramatically increased to 80%.

Next, we investigated the reactions of several 1,3-dicarbonyl compounds to alkenes such as α-methylstyrene, exo olefins, vinyl ether, and vinyl sulfide. The results are summarized in Table 2. In the ^1H NMR spectra, the synthesized dihydrofurans are identified by the chemical shifts associated with a methylene group of the dihydrofuran ring.[12] In the case of entries 1-5, only a single product was seen. In entries 6-9, both the *cis* and *trans* products were obtained in good yield. The stereochemical assignment of *cis*- and *trans*-isomers was defined by observation of the coupling constants between vicinal protons.

Table 1. Effect of Silver(I) Metals and Solvents in the Reaction of 1,3-Cyclohexanedione with Vinyl ether.



silver(I)	solvent	temp.	time(h)	yield(%)
$AgNO_3$	acetonitrile	reflux	5	0
AgOAc	acetonitrile	reflux	5	0
$AgBF_4$	acetonitrile	reflux	5	0
Ag_2CO_3	acetonitrile	reflux	5	70
Ag_2CO_3/ Celite	acetonitrile	reflux	3	78
Ag_2CO_3/ silica gel	acetonitrile	reflux	2	31
Ag_2O	acetonitrile	reflux	4	69
Ag_2O/ Celite	acetonitrile	reflux	2	80
Ag_2O/ Celite	DMSO	80 ℃	1.5	46
Ag_2O/ Celite	DMF	80 ℃	1.5	36
Ag_2O/ Celite	benzene	reflux	4	15
Ag_2O/ Celite	heptane	reflux	4	10

In spite of the widespread use of a number of metal oxidants, there is no direct precedent for metal mediated oxidative cycloaddition of 1,3-dicarbonyl compounds to olefins such as entries 4 and 6-9. In particular, application of this reaction led to the synthesis of furanocoumarin **10** and furoquinolinone **11**, which were known to have anthelmintic, hypnotic, antifungal, and anticoagulant activities.[13]

Although the exact mechanism of the reaction is not clear, this result is best described as in Scheme 1. The 1,3-dicarbonyl compound **1** is first oxidized by silver(I) metal to generate the α-oxoalkyl radical **12**, which then attacks the olefin to give the radical **13**. The nucleophilic adduct **13** now undergoes fast oxidation by silver(I) to a carbonium ion **14** which cyclizes to the desired dihydrofuran **15**.

In summary, the silver(I)/Celite mediated oxidative addition of 1,3-dicarbonyl compounds to olefins such as vinyl ether and vinyl sulfide offers a facile and simple method for the synthesis of substituted dihydrofurans. Further mechanistic studies and application of this reaction will be investigated, now in progress in our laboratory.

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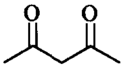
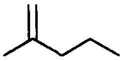
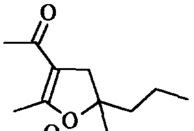
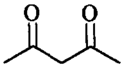
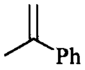
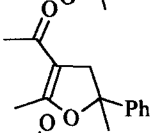
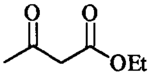
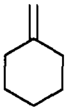
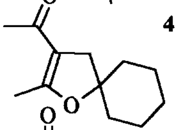
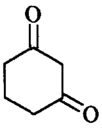
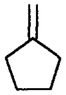
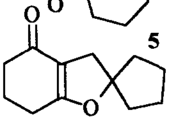
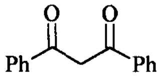
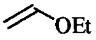
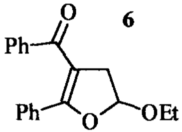
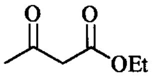
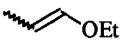
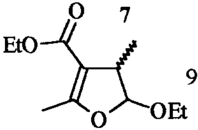
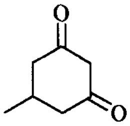
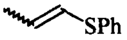
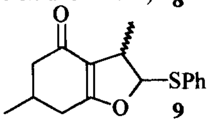
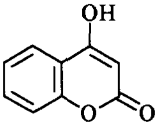
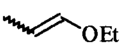
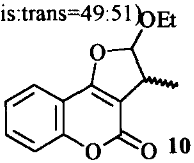
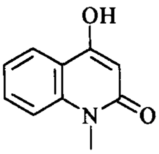
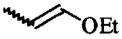
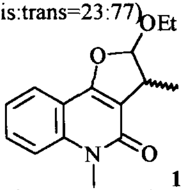
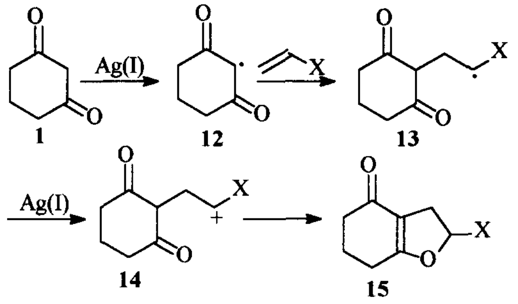
Table 2. Synthesis of Dihydrofurans

Entry	1,3-Dicarbonyl compound	Olefin	Silver(I)/Celite	Product	Yield
1			Ag_2CO_3	 **3**	89
2			Ag_2CO_3	 **4**	91
3			Ag_2CO_3	 **5**	56
4			Ag_2CO_3	 **6**	72
5			Ag_2O	 **7**	89
6		 (cis:trans=75:25)	Ag_2CO_3	 (cis:trans=47:53) **8**	92
7		 (cis:trans=62:38)	Ag_2CO_3	 **9** (cis:trans=49:51)	86
8		 (cis:trans=75:25)	Ag_2CO_3	 **10** (cis:trans=23:77)	66
9		 (cis:trans=75:25)	Ag_2CO_3	 **11** (cis:trans=17:83)	55



Scheme 1

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12. Spectral data for **3**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.71(2H, m), 2.19 (3H, s), 2.18 (3H, s), 1.60 (2H, t, J=7.3 Hz), 1.40-1.30 (2H, m), 1.33 (3H, s), 0.93 (3H, t, J=7.3 Hz); IR (neat) 2951, 2873, 1669, 1606, 1443, 1380, 1279, 1241, 1199, 1146, 1025, 978, 937 cm^{-1}. **4:** ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37-7.28 (5H, m), 3.14 (2H, m), 2.33 (3H, s), 2.19 (3H, s), 1.69 (3H, s); IR (neat) 3060, 2978, 1671, 1608, 1495, 1444, 1381, 1246, 1158, 1069, 937, 765 cm^{-1}. **5:** ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.13 (2H, q, J=7.0 Hz), 2.59 (2H, s), 2.13 (3H, s), 1.64-1.40 (10H, m), 1.25 (3H, t, J=7.1 Hz); IR (neat) 2934, 2859, 1698, 1645, 1449, 1383, 1337, 1302, 1277, 1233, 1128, 1082, 1032, 978, 961 cm^{-1}. **6:** ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.76 (2H, s), 2.33 (4H, m), 2.02 (4H, m), 1.70 (6H, m); IR (neat) 2951, 2872, 1630, 1453, 1424, 1404, 1372, 1341, 1259, 1181, 1138, 1061, 1005, 953, 897 cm^{-1}. **7:** H NMR (300 MHz, CDCl$_3$) δ 7.48-7.07 (10H, m), 5.75 (1H, dd, J=7.5, 2.7 Hz), 4.03 (1H, m), 3.74 (1H, m), 3.50 (1H, dd, J=14.3, 7.5 Hz), 3.09 (1H, dd, J=13.8, 2.7 Hz), 1.33 (3H, t, J= 6.9 Hz); IR (neat) 3061, 2978, 2932, 1614, 1574, 1491, 1446, 1367, 1248, 1198, 1090, 1069, 984, 883 cm^{-1}. **8:** ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.48 (*cis*, 0.47H, J=7. 6 Hz) and 5.04 (*trans*, 0.53H, J=1.6 Hz), 4.17 (2H, m), 3.85 (1H, m), 3.57 (1H, m), 3.20 (*cis*, 0.47H, m), 2.96 (*trans*, 0.53H, m), 2.22 and 2.19 (3H, s), 1.29 (2H, m), 1.22(3H, d); IR (neat) 2980, 2934, 1701, 1649, 1448, 1381, 1327, 1255, 1219, 1078, 999, 951 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), 1.11 (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 7.62 (1H, d, J=7.7 Hz), 7.49 (1H, d, J=8.5 Hz), 7.31 (1H, d, J=8.3 Hz), 7.22 (1H, d, J=7.6Hz), 5.91 (*cis*, 0.23H, d, J=7.3 Hz) and 5.52(*trans*, 0.77H, d, J=2.6 Hz), 3.95 (1H, m), 3.69 (1H, m), 3.51 (*cis*, 0.23H, m) and 3.28 (*trans*, 0.77H, m), 1.32 (3H, d, J=7.2Hz), 1.24 (3H, m); IR (KBr) 3067, 2980, 2935, 1720, 1647, 1609, 1570, 1501, 1454, 1412, 1379, 1348, 1271, 1246, 1207, 1119, 1059, 1030, 978 cm^{-1}. **11:** ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.79 (1H, d, J=7.8 Hz), 7.57 (1H, d, J=8.3 Hz), 7.36 (1H, d, J=8.6 Hz), 7.25 (1H, d, J=7.4 Hz), 5.90 (*cis*, 0.17H, d, J=7.3 Hz) and 5.52 (*trans*, 0.83H, d, J=2.2 Hz), 4.02 (1H, m), 3.75 (1H, m), 3.69 (3H, s), 3.68 (*cis*, 0.17H, m) and 3.42 (*trans*, 0.83H, m), 1.39 (3H, d, J=7.2 Hz), 1.29 (3H, m); IR (neat) 2978, 2934, 1659, 1595, 1570, 1508, 1460, 1421, 1354, 1290, 1244, 1095, 1047, 922 cm^{-1}.
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