$Mo(CO)_6$ Catalyzed One-Pot Conversion of Allyl Aryl Ethers to Dihydrobenzofurans

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Molybdenum hexacarbonyl effectively catalyses a tandem Claisen rearrangement-cyclization reaction of allyl aryl ethers to give good yields of dihydrobenzofurans.

Molybdenum hexacarbonyl has recently gained increasing importance as a practical reagent that can be used as an effective catalyst in several reactions. It has been used successfully in cyclization of alkynols and epoxyalkynes[1] to 2,3-dihydrofurans and furans, respectively, in reductive coupling of allyl acetates,[2] in elimination of allylic acetates[3] and in the desulfenylative allylation of allylic sulfides.[4] Molybdenum catalyzed allylic alkylations have been recently reported by Trost[5] as a useful means to provide regiochemical alternatives to the analogous palladium catalyzed reactions. To the best of our knowledge the Lewis acid properties of molybdenum hexacarbonyl have been reported only in a few papers,[6-8] where it has been used in Friedel-Crafts reactions. No examples of the use of this reagent in Claisen rearrangement cyclization reaction of allyl aryl ethers to dihydrobenzofurans can be found.

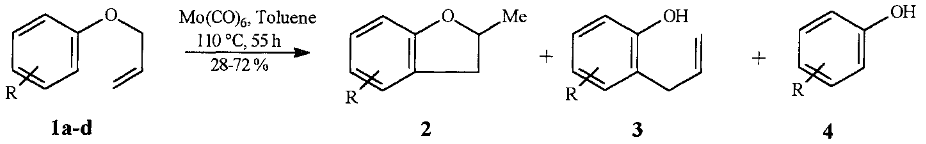
The dihydrobenzofurans, which are important intermediates in natural products chemistry,[9] are generally prepared in two steps from allyl aryl ethers by the Claisen rearrangement[10] followed by cyclization of the resulting *ortho*-allyl phenols with strong acids.[11] Two recent methods have reported a synthetically exploitable one-step synthesis of dihydrobenzofurans, through a tandem Claisen rearrangement-cyclization reaction of allyl aryl ethers, using $ZnCl_2$ at 140°C in decalin[12] or $AlCl_3$ at -70°C in dichloromethane,[13] respectively.

Here we wish to report a new use of $Mo(CO)_6$ as a catalyst in a one-pot Claisen rearrangement-cyclization reaction of the allyl aryl ethers **1**, to give the corresponding dihydrobenzofurans,[14] in yields ranging from moderate to excellent (Tables 1 and 2). A variety of experimental conditions were tested changing the solvent, the reaction time and the amount of catalyst. The best results were obtained when the reaction was carried out in refluxing toluene, in a Schlenk flask stoppered with a rubber septum under argon for 55 h, while no reaction took place in the presence of air or in solvents such as dioxane or dimethylformamide.

The substitution pattern of the allylic moiety was crucial in determining the amount of $Mo(CO)_6$ to be used to obtain the best conversion of the starting allyl aryl ethers. It was found that using 40% mol of catalyst the allyl aryl ethers **1a–d** (entries 1, 3, 5, 7, Table 1) gave low to medium yields of 2,3-dihydro-2-methyl benzofurans **2** always accompanied by variable amounts of *ortho*-allyl phenols **3** and phenols **4** together with unreacted starting material. On the other hand the aryl methallyl ethers **1e–q**, under the same reaction conditions, led to 2,3-dihydro-2,2-dimethyl benzofurans **5** usually in good to excellent yields and often as the only detectable products (entries 3, 6, 9, 12–14, Table 2). Low yields were obtained in reactions of **1h, 1l, 1n** (entries 4, 7, 10, Table 2) and, in these cases, the dihydrobenzofurans were accompanied by some unreacted starting material, the corresponding phenols and variable amounts of aryl[(2-methylprop-1-enyl)oxy] derivatives **6**. These products have been isolated by column chromatography and identified by the characteristic presence of the vinylic proton at $\delta = 6.1$ and the two methyl singlets between $\delta = 1.65$ and 1.75 in their ^1H NMR spectra.

The use of catalyst/allyl ether in a 1:1 molar ratio led to 87–100% of conversion of derivatives **1a–d** (entries 2, 4, 6, 8, Table 1) and to 100% of conversion of **1h, 1l, 1n** (entries 5, 8, 11, Table 2).

The reaction appears to be favoured by the presence of *para* electron-donating substituents (**1b, 1c**, Table 1; **1f, 1g, 1o–q**, Table 2), while *para* electron-withdrawing groups (**1d, 1n**) decrease the cyclization rate. The presence of *ortho* substituents (**1h, 1l**), probably as a consequence of a steric hindrance, led to low yields of the corresponding dihydrobenzofurans. A moderate regiocontrol favours the formation of the less hindered 2,2,6-trimethyldihydrobenzofuran over the alternative 2,2,4



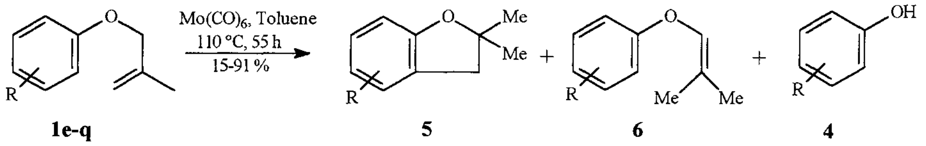


Table 1. Claisen Rearrangement-Cyclization of Allyl Aryl Ethers **1a–d**

Entry	Substrate	R	$Mo(CO)_6$ (mol %)	Yield (%)[a]	Product Distribution[b]			
					2	**3**	**4**	Starting Material
1	**1a**	H	40	75 (28)	40	12	7	41
2	**1a**	H	100	83 (62)	78	10		12
3	**1b**	4-Me	40	68 (35)	55	15	2	28
4	**1b**	4-Me	100	75 (60)	82	6	4	8
5	**1c**	4-OMe	40	90 (65)	74	20	1	5
6	**1c**	4-OMe	100	75 (72)	> 98			
7	**1d**	4-Cl	40	98 (32)	36	10	2	52
8	**1d**	4-Cl	100	98 (65)	70	9	8	13

[a] Yield of the isolated crude product mixture. Yield of isolated pure **2** is given in parenthesis.

[b] Determined by ^{1}H NMR (300 MHz) and GC/MS analyses of the crude product mixture.

Table 2. Claisen Rearrangement-Cyclization of Methallyl Aryl Ethers **1e–q**

Entry	Substrate	R	$Mo(CO)_6$ (mol %)	Yield (%)[a]	Product Distribution[b]			
					5	**6**	**4**	Starting Material
1	**1e**	H	40	95 (70)	75		25	
2	**1f**	4-Me	40	83 (70)	86	12	2	
3	**1g**	4-OMe	40	94 (91)	> 98			
4	**1h**	2-Me	40	70 (12)	20	26	3	51
5	**1h**	2-Me	100	88 (50)	60	3	37	
6	**1i**	3-Me	40	75 (70)	> 98[c]			
7	**1l**	2,4-Me	40	67 (25)	45	18	14	23
8	**1l**	2,4-Me	100	90 (60)	72		28	
9	**1m**	3,5-Me	40	88 (85)	> 98			
10	**1n**	4-Br	40	96 (15)	19	28	3	50
11	**1n**	4-Br	100	97 (65)	72	19	9	
12	**1o**	4-Et	40	75 (72)	> 98			
13	**1p**	4-*i*-Pr	40	73 (70)	> 98			
14	**1q**	4-*t*-Bu	40	78 (75)	> 98		28	

[a] Yield of the isolated crude product mixture. Yield of isolated pure **5** is given in parenthesis.

[b] Determined by ^{1}H NMR (300 MHz) and GC/MS analyses of the crude product mixture.

[c] A 70 : 30 mixture of 2,2,6-trimethyl- and 2,2,4-trimethyl-2,3-dihydrobenzofurans.

trimethyl derivative (entry 6, Table 2). The *ortho*-allyl phenols, often present in the reaction mixtures of **1a–d**, appear to be true reaction intermediates in this synthesis of the dihydrobenzofurans, as demonstrated by the fact that the *ortho*-allyl phenol **3a** itself when treated with 40% moles of $Mo(CO)_6$, in the usual conditions, gave the 2,3-dihydro-2-methylbenzofuran (**2a**) in 35% yield.

Concerning the nature of the catalytic species, it is well known that $Mo(CO)_6$ in toluene is readily converted in situ to $TolMo(CO)_3$, considered to be the true catalyst or a catalyst precursor in Friedel–Crafts reactions.[7] The observation that our reactions occur only if they are run in a stoppered Schlenk flask, together with the fact that the interchange of the arene and the CO groups is a reversible reaction,[15] makes it feasible that the catalyst of this reaction is neither $Mo(CO)_6$ nor $TolMo(CO)_3$, but both of them in equilibrium. It is possible that, during the replacement of the arene ring by the CO groups or in the inverse process, the oxygen atom of the allyl aryl ethers can successfully compete with them and consequently coordinate with the metal occupying one or more electrophilic centres. The so formed new complex can cleave with loss of an allyl cation or undergo a [3,3]-rearrangement, triggering an intermolecular or intramolecular Claisen rearrangement-cyclization.

In conclusion, the simplicity of the reaction and its work-up, together with the low cost of $Mo(CO)_6$ and the stability of the reagent which greatly facilitates its handling in comparison with other Lewis acids, makes it a very convenient and promising catalyst for the synthesis of dihydrobenzofurans. Further investigations are being carried out on the Lewis acid properties of $Mo(CO)_6$ and the results will be published in due course.

Reagent-grade commercially available reagents and solvents were used. Toluene was freshly distilled from sodium. $Mo(CO)_6$ was used as received from Aldrich Chemistry. Column chromatography was performed with Fluka silica gel (70–230 mesh). The allyl aryl ether **1a** is commercially available, while **1b,d**,[16] **1c**,[17] **1e,f,h,m**,[13] **1g,n**,[18] **1i**,[19] have been previously described. The dihydrobenzofurans **2a**,[20] **2b**,[21] **2c**,[22] **2d**,[23] **5e,f,h,m**,[13] **5g**,[24] **5i**,[25] **5q**[26] have already been reported. Allyl phenol **3a** was commercially available while the phenols **3b–d**,[23] and the aryl[(2-methylprop-1-enyl)oxy] derivatives **6f,n**[18] have been previously reported. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity 300 spectrometer using CDCl$_3$ solutions: chemical shifts are reported in ppm from TMS as internal standard and are given in δ units. Mass spectra were obtained by EI (70 eV) using a mass spectrometer HP 5989A equipped with a GC HP 5890. Elemental analyses, carried out on a Carlo Erba model 1106 Element analyzer, gave satisfactory results: C, H = ± 0.3 %.

Allyl Aryl Ethers 1o–q; General Procedure:

A mixture of the phenol (0.1 mol), the allyl halide (0.1 mol) and K$_2$CO$_3$ (12.8 g, 0.1 mol) in acetone (60 mL) was heated under reflux for 15 h. The mixture was then poured into water (50 mL) and extracted with CH$_2$Cl$_2$ (2×50 mL). The organic layer was washed with 10 % NaOH solution (2×50 mL), H$_2$O and brine. After drying (Na$_2$SO$_4$) and filtration the solution was concentrated to afford the corresponding allyl aryl ether, which was purified by vacuum distillation; Yield: 70–90 %.

4-Ethylphenyl Methallyl Ether **(1o)**: Yield 70 %; bp 68 °C/0.1 Torr.

^{1}H NMR (CDCl$_3$): $\delta = 1.29$ (t, 3 H, $J = 7.8$ Hz), 1.90 (s, 3 H), 2.66 (q, 2 H, $J = 7.8$ Hz), 4.47 (s, 2 H), 5.05 (d, 1 H, $J = 0.9$ Hz), 5.32 (d, 1 H, $J = 0.9$ Hz), 7.09–7.22 (m, 4 H).

Methallyl 4-i-Propylphenyl Ether **(1p)**: Yield 72 %; bp 68–70 °C/ 0.1 Torr.

^{1}H NMR (CDCl$_3$): $\delta = 1.45$ (d, 6 H, $J = 6.9$ Hz), 2.04 (s, 3 H), 3.07 (m, 1 H), 4.61 (s, 2 H), 5.19 (br s, 1 H), 5.32 (br s, 1 H), 7.06–7.36 (m, 4 H).

4-t-Butylphenyl Methallyl Ether **(1q)**: Yield 75 %; bp 78–80 °C/ 0.2 Torr.

^{1}H NMR (CDCl$_3$): $\delta = 1.31$ (s, 9 H), 1.83 (s, 3 H), 4.41 (s, 2 H), 4.98 (d, 1 H, $J = 0.7$ Hz), 5.11 (d, 1 H, $J = 0.7$ Hz).

2,3-Dihydrobenzofurans 2a–d, 5e–q; General Procedure:

A solution of allyl aryl ether **1a–q** (3–5 mmol) in toluene (6–10 mL) containing Mo(CO)$_6$ (40 or 100 mol%), kept under argon in a stoppered Schlenk flask, was stirred at 115 °C (external oil bath temperature) for 55 h. Then Et$_2$O (10 mL) was added to the cooled solution, which was filtered through Al$_2$O$_3$ and concentrated in vacuo. The product distribution was determined by GC/MS and ^{1}H NMR analyses of the crude mixture. After elimination of the phenolic fraction by extraction with 10% NaOH solution (2×5 mL), the mixture was chromatographed on a silica gel column using light petroleum as eluent. Products **2a–d, 5e–i, 5m, 5q, 6f, 6n** were easily identified by comparison of their physical and spectroscopic properties with the reported literature data. The easily identified signals in their NMR spectra allowed unequivocal characterization of new compounds **5l, 5n–p, 6h, 6l.**

2,3-Dihydro-2,2,5,7-tetramethylbenzofuran **(5l)**:

^{1}H NMR (CDCl$_3$): $\delta = 1.44$ (s, 6 H), 2.15 (s, 3 H, 2.22 (s, 3 H), 2.94 (s, 2 H), 6.60–6.94 (m, 2 H).

^{13}C NMR (CDCl$_3$): $\delta = 15.29$, 20.68, 28.29, 28.57, 43.22, 85.79, 119.03, 122.90, 126.26, 128.86, 129.62, 155.27.

5-Bromo-2,3-dihydro-2,2-dimethylbenzofuran **(5n)**:

^{1}H NMR (CDCl$_3$): $\delta = 1.44$ (s, 6 H), 2.15 (s, 3 H), 2.22 (s, 3 H), 2.94 (s, 2 H), 6.78–7.37 (m, 3 H).

^{13}C NMR (CDCl$_3$): $\delta = 28.01$, 42.60, 87.41, 110.97, 129.53, 130.64, 132.12, 140.40, 157.94.

5-Ethyl-2,3-dihydro-2,2-dimethylbenzofuran **(5o)**:

^{1}H NMR (CDCl$_3$): $\delta = 1.10$ (t, 3 H, $J = 7.5$ Hz), 1.35 (s, 6 H), 2.46 (q, 2 H, $J = 7.5$ Hz), 2.86 (s, 2 H), 6.80–6.86 (m, 3 H).

^{13}C NMR (CDCl$_3$): $\delta = 16.15$, 28.18, 28.27, 42.91, 86.31, 108.99, 124.50, 126.96, 127.12, 135.81, 156.84.

2,3-Dihydro-2,2-dimethyl-5-(i-propyl)benzofuran **(5p)**:

^{1}H NMR (CDCl$_3$): $\delta = 1.21$ (d, 6 H, $J = 6.8$ Hz), 1.45 (s, 6), 2.82 (m, 1 H), 2.98 (s, 2 H), 6.80–6.95 (m, 3 H).

^{13}C NMR (CDCl$_3$): $\delta = 24.20$, 24.29, 28.23, 33.53, 42.96, 86.41, 108.94, 123.01, 125.74, 126.86, 127.34, 140.60.

1-Methyl-2-[(2-methylprop-1-enyl)oxy]benzene **(6h)**:

^{1}H NMR (CDCl$_3$): $\delta = 1.70$ (s, 3 H), 1.75 (s, 3 H), 2.23 (s, 3 H), 6.15 (m, 1 H), 6.70–7.25 (m, 4 H).

1,3-Dimethyl-4-[(2-methylprop-1-enyl)oxy]benzene **(6l)**:

^{1}H NMR (CDCl$_3$): $\delta = 1.67$ (s, 3 H), 1.72 (s, 3 H), 2.16 (s, 3 H), 2.29 (s, 3 H), 6.15 (m, 1 H), 6.62–6.94 (m, 3 H).

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(1) McDonald, F. E.; Schultz, C.C. *J. Am. Chem. Soc.* **1994**, *116*, 9363.
(2) Masuyama, Y.; Otake, K.; Kurusu, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1527.
(3) Balde, R.J.; Robinson, J.E. *tetrahedron Lett.* **1986**, *27*, 3209.
(4) Musuyama, Y.; Yamada, K.; Kurusu, Y. *Tetrahedron Lett.* **1987**, *28*, 443.
(5) Trost, B.M.; Merlic, C.A. *J. Org. Chem.* **1990**, *55*, 1127.
Trost, B.M.; Lautens, M. *J. Am. Chem. Soc.* **1987**, *109*, 1469.
Trost, B.M.; Lautens, M. *Tetrahedron* **1987**, *43*, 4817.
(6) Trost, B.M.; Ghadiri, M.R. *J. Am. Chem. Soc.* **1984**, *106*, 7260.
(7) White, J.F.; Farona, M.F. *J. Organometal. Chem.* **1973**, *63*, 329.
(8) White, J.F.; Farona, M.F. *J. Am. Chem. Soc.* **1971**, *93*, 2826.
(9) Dean, F.M. In *Naturally Occurring Oxygen Ring Compounds*; Butterworths: London, 1963; p 135.
Cagniant, P.; Cagniant, D. *Adv. Heterocycl. Chem.* **1975**, *18*, 358.
(10) For reviews on the Claisen rearrangement see:
Bennett, G.B. *Synthesis* **1977**, 589.
Lutz, R.P. *Chem. Rev.* **1984**, *84*, 205.
(11) Shulgin, A.T.; Baker, A.W. *J. Org. Chem.* **1963**, *28*, 2468.
Harwood, L.M. *J. Chem. Soc., Chem. Commun.* **1982**, 1120.
Harwood, L.M. *J. Chem. Soc., Chem. Commun.* **1983**, 530.
Widmer, U.; Hansen, H.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2644.
Nichols, D.E.; Hoffman, A.J.; Oberlender, R.A.; Riggs, R.A. *J. Med. Chem.* **1986**, *29*, 302.
(12) Feoktistov, V.M.; Bunina-Drivorukova, L.I.; Bal'yan, Zh. V. *Zh. Org. Khim.* **1978**, *14*, 807; *Chem. Abstr.* **1978**, *89*, 59734.
(13) Kim, K.M.; Kim, H.R.; Ryu, E.K. *Heterocycles* **1993**, *36*, 497.
Kim, K.M.; Kim, H.R.; Chung, K.H.; Song, J.H.; Ryu, E.K. *Synth. Commun.* **1994**, *24*, 1859.
(14) Analogous reaction on the crotyl phenyl ether led to a complex reaction mixture where the two products coming from the Claisen rearrangement, the 2-(1-methylprop-2-enyl)- and the 2-(but-2-enyl)phenols, were present as major products in 30–35 % yields as evaluated by ^{1}H NMR and mass spectra.
(15) Fischer, E.O.; Öfele, K. *Chem. Ber.* **1957**, *90*, 2532; *ibid.* **1958**, *91*, 2763.
Fischer, E.O.; Öfele, K. *Angew. Chem.* **1957**, *69*, 715.
(16) Borguya, T.; Madeja, R.; Gahrni, P.; Hansen, H.J.; Schmid, H.; Barner, R. *Helv. Chim. Acta* **1973**, *56*, 14.
(17) Takahashi, T.; Senda, S. *J. Pharm. Soc. Jpn.* **1949**, *69*, 498.
(18) Julia, M.; Baillerge, M. *Bull. Soc. Chim. Fr.* **1966**, *2*, 734.
(19) Bartz, Q.R.; Miller, R.F.; Adams, R. *J. Am. Chem. Soc.* **1935**, *57*, 371.
(20) Gripenberg, J.; Hase, T. *Acta. Chem. Scand.* **1966**, *20*, 1561.
(21) Speziale, V.; Dao, H.G.; Lattes, A. *J. Heterocycl. Chem.* **1978**, 225.
(22) Royer, R.; Demerseman, P.; Rossingnol, J.-F. *Bull. Soc. Chim. Fr.* **1971**, *6*, 2072.
(23) Geresh, S.; Levy, O.; Markovits, Y.; Shani, A. *Tetrahedron* **1975**, *31*, 2803.
(24) Ariamala, G.; Balasubramanian, K.K. *Tetrahedron* **1989**, *45*, 3769.
(25) Marini, J.C.; Franke, N.W.; Singerman, G.H. *J. Org. Chem.* **1970**, *35*, 2904.
(26) Arduini, A.; Pochini, A.; Ungaro, R. *Synthesis* **1984**, 950.