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Mo(CO)$_6$/TBHP Catalyzed Autoxidation of 5-Alkylidene-4,5-Dihydrofurans

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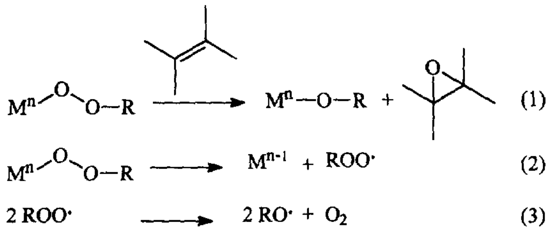
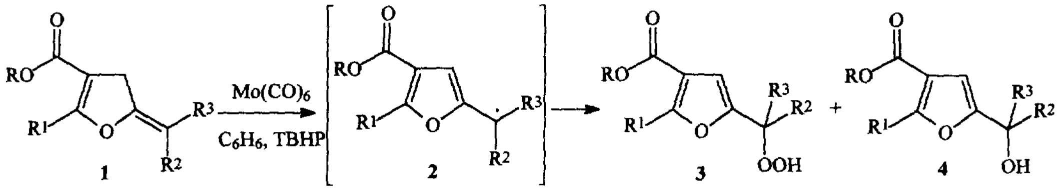
Abstract: Mo(CO)$_6$/*t*-butyl hydroperoxide, well known to epoxidize olefins, was shown to be a mild and very efficient system for the autoxidation of 5-alkylidene-4,5-dihydrofurans. High yields of primary, secondary and tertiary furyl hydroperoxides have been achieved employing catalytic amount of Mo(CO)$_6$. A radical mechanism is in agreement with the experimental data.

Epoxidation of olefins represents one of the fundamental processes in preparative organic synthesis.[1] Early transition metal compounds (e.g., Mo, Ti, W and V), in combination with hydrogen peroxide or alkyl hydroperoxides, can be considered the most popular catalytic systems.[2] In particular, soluble molybdenum compounds satisfy the requirements to be active and selective epoxidation catalysts. In fact, they act as strong Lewis acids (Scheme 1) increasing the electrophilic character of the peroxidic oxygens and, furthermore act as weak oxidants in their highest oxidation state. This reduces the competing one electron oxidation of the ROO ligand[3] (Scheme 1, eq. 2).



Scheme 1

A set of preliminary experiments, performed on 5-alkylidene-4,5-dihydrofurans[4] of type **1** pointed out a different behaviour of the Mo(CO)$_6$-TBHP catalytic system. Under the conditions reported for the representative starting compound **1a** (R=Et, R^1=R^2=Me, R^3=H, Scheme 2, Table 1) the formation of hydroperoxide[5] **3** proved to be the favoured process.



Scheme 2

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Table 1. Mo(CO)$_6$-TBHP catalyzed autoxidation of 1a

Entry	TBHP (eq)	Mo(CO)$_6$ (%mol)	T(°C)	t (h)	3 (%)[a]	4 (%)[a]
1[b]	2	6	40	2.5	60	31
2[b]	2	3	"	8	66	-
3[c]	-	6	"	18	5	2
4[d]	2	-	"	6.5	20	-

[a]Yields were evaluated on the basis of ^{1}H-NMR data, only compounds **1**, **3**, **4** were present at the end of reaction. [b]The reaction was conducted under air. [c]The reaction was conducted under O_2 atmosphere. [d]The reaction was conducted under an argon atmosphere.

Alkylidene **1a**, treated with a small amount of Mo(CO)$_6$ (6% mol, entry 1) in benzene with 2 eq. of TBHP, was easily converted to hydroperoxide **3a** in good yield contaminated by 31% of furyl alcohol **4a**. Lowering the amount of catalyst (entry 2) improved the yield of **3a** and none of the decomposition compound **4a** was detected. In absence of TBHP and under oxygen atmosphere (entry 3) **1a** was recovered after prolonged time, while without catalyst only a small amount of furyl hydroperoxide **3a** was produced (last entry). These results clearly showed that Mo(CO)$_6$-TBHP could be a suitable system to oxidize compounds **1**, so we enlarged the investigation, optimizing the reaction conditions[6] (Table 2). Furyl hydroperoxides **3** can be synthetically useful in the Sharpless-modified asymmetric sulfoxidation[7] (ee 60-95%) and in the kinetic resolution of racemic sulfoxides[8] (ee 42-> 95%), as alternative and superior reagents to the commercial TBHP and CHP.

Catalytic amounts of Mo(CO)$_6$ (1% mol) and 2 eq of TBHP with respect to **1** under air accomplished almost complete conversion of **1** to tertiary, secondary and primary furyl hydroperoxides **3**. Interestingly, because of mild conditions, we isolated compounds **3** in high yields without any traces of compounds **4**, furyl ketones or aldehydes. These results were unexpected[9] especially for primary hydroperoxides (entries 5 and 6), which are difficult to synthesize. Higher temperature, as predicted, reduced the reaction time but at the expense of hydroperoxide decomposition (entry 7). *n*-Hexane can also be used as an alternative solvent (entries 8-10).

Table 2. Mo(CO)$_6$-TBHP catalyzed autoxidation of 1[a]

Entry	1	Mo(CO)$_6$ (%mol)	Solvent	T (°C)	t (h)	3 (%)[b]	4 (%)[b]
1	**1a**	1	C_6H_6	40	6	73	-
2	$R=Et, R^3=H, R^1=i\text{-}Pr, R^2=Me$ **1b**	"	"	"	5.5	84	-
3	$R=R^1=\text{-}(CH_2)_3\text{-}, R^2=Me, R^3=H$ **1c**	"	"	"	"	73	-
4	$R=Et, R^3=Me, R^1=R^2=Me$ **1d**	"	"	"	5	84	-
5	$R=Et, R^3=R^2=H, R^1=Me$ **1e**	"	"	50	7	86	-
6	$R=R^1=\text{-}(CH_2)_3\text{-}, R^2= R^3=H$ **1f**	"	"	"	15	87	-
7	**1a**	"	"	70	2	60	25
8	**1a**	"	*n*-hexane	50	6	76	-
9	**1b**	1.5	"	"	4.5	97	-
10	**1e**	1	"	"	7.5	88	-

[a]All the reactions were conducted with the following molar ratios 1/TBHP 1/2 under air. [b]Isolated yields based on **1**.

In order to elucidate if a radical process was involved, we ran additional experiments (Table 3). Complete conversion to hydroperoxide **3a**, in reduced reaction time, was found by bubbling oxygen into the reaction vessel (compare entry 1 with entry 1 in Table 2). Employing only 0.4 eq. of TBHP with respect to **1a** and bubbling oxygen, although for a longer reaction time, gave **3a** in good yield. Finally, under argon atmosphere the conversion to **3a** was greatly slowed down (compare entry 3 with entry 1 in Table 2). So the presence of oxygen strongly affected the rate of the reaction and the yield of hydroperoxide.

Table3. Influence of different parameters on $Mo(CO)_6$-TBHP catalyzed autoxidation of 1 in C_6H_6[a]

Entry	1	Scavenger	TBHP (eq)	T (°C)	t (h)	**3** (%)[b]	**4** (%)[b]
1[c]	**1a**	-	2	40	3	96	-
2[c]	"	-	0.4	"	22	73	20
3[d]	"	-	2	"	6	18	22
4[e]	"	2,4,6-tri-*tert*-butyl phenol	2	"	23	-	34

[a]All the reactions were carried out with 1% mol of $Mo(CO)_6$ with respect to **1** and molar ratios **1**/TBHP= 1/2. [b]Yields were evaluated on the basis of ^{1}H-NMR data. [c]The experiment was conducted by bubbling O_2 in the reaction vessel.[d]The reaction was conducted under an argon atmosphere. [e]The reaction was conducted under air in presence of 1 eq of 2,4,6-tri-*tert*-butyl phenol respect to **1a**.

Inhibition of the oxidation was observed in the presence of the radical scavenger 2,4,6-tri-*tert*-butylphenol, recently shown as an efficient trap[10] for *tert*-butylperoxyl radicals (entry 4). About 60% of starting **1a** and 34% of furyl alcohol **4a** were detected in the crude mixture after prolonged time.

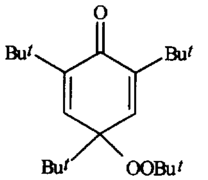

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Figure 1

Furthermore, ^{1}H-NMR spectra indicated the presence of an additional compound (Figure 1), the peroxyl adduct **5** which confirms the involvement of *tert*-butyl peroxyl radicals[11] in the process.

This result is in agreement with the proposal of homolytic $Mo(CO)_6$ induced decomposition of TBHP reported in Scheme 1 (eq. 2). Then, *tert*-butylperoxyl radicals acts as radical initiators for the autoxidation of the 5-alkylidene-4,5-dihydrofuran, giving rise to radicals **2** that can be captured by oxygen (derived from *tert*-butylperoxyl radicals self-reaction, eq. 3 in Scheme 1 and from air) to furnish furyl hydroperoxides **3** as was reported in Scheme 2. Furthermore, a strong influence of oxygen is clearly expected as is shown in Table 3.

In conclusion we have found that $Mo(CO)_6$-TBHP system is able to promote the autoxidation of 5-alkylidene-4,5-dihydrofurans **1**. The mild and flexibile reaction conditions allows the preparation of primary, secondary and tertiary furyl hydroperoxides with a superior efficiency compared to the previous methodologies[5] used for their synthesis.

Acknowledgments

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6. *Typical experimental procedure*: to a solution of **1** (1 mmol) in 12 mL of benzene or *n*-hexane is added $Mo(CO)_6$ (1% mol) and TBHP (2 mmol, 5 M solution in decane) at 40-50°C and stirring is maintained until the disappearance of **1** as monitored by TLC. After removal of the solvent *in vacuo*, flash chromatography of the residue in mixtures of petroleum ether-diethyl ether afforded furyl hydroperoxides **3**. Spectroscopic data of **3** are reported in the literature (ref. 5b).
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9. While catalytic amounts of $Mo(CO)_6$ induces homolytic decomposition of TBHP, furyl hydroperoxides **3** are unaffected in the mentioned conditions. They are less prone to suffer metal decomposition, probably because of their intrinsic higher chemical stability. For more insight into metal-induced decomposition of primary, secondary and tertiary alkyl hydroperoxides see: Hiatt, R.; Irwin, K. C.; Gould, C. W. *J. Org. Chem.* **1968**, *33*, 1430.
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11. As a confirmation, a blank experiment with 2,4,6-tri-*tert*-butyl phenol (1eq.) ($Mo(CO)_6$ (1% mol) and TBHP (2eq.) was conducted in the absence of **1a** under air in benzene at 40°C, after 20 h the radical adduct **5** was isolated in 85% yield (based on the phenol).