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Novel Highly Regioselective $VO(acac)_2$/TBHP Mediated Oxidation of *o*-Alkenyl Phenols to *o*-Hydroxybenzyl Ketones

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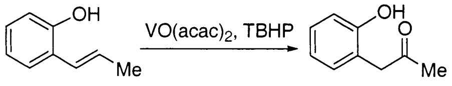
Abstract: A novel mild methodology for the preparation of *o*-hydroxybenzyl ketones is described starting from *o*-alkenyl phenols and based on the $VO(acac)_2$/TBHP (2 mol %/1.2 equiv) system. $VO(acac)_2$ first catalyzes the epoxidation of *o*-alkenyl phenols and then the rearrangement of the epoxyphenols to ketones via the selective benzylic C−O cleavage and 1,2 hydride migration. The protocol has also been applied to set up a useful and easy one-pot conversion of *o*-alkenyl phenols to benzo[*b*]furans by means of the sequential addition of TFA, after the generation of the intermediate *o*-hydroxybenzyl ketones.

The development of catalytic and selective methods of oxidation is extremely important in organic synthesis. Among the several oxidizing reagents,[1] the metal-catalyzed methodologies[2] have experienced ever increasing growth and application over the years. One of the best examples reported so far is the $VO(acac)_2$/TBHP system. First employed by Sharpless in the highly regio- and stereoselective epoxidation of allylic alcohols,[3] it has been successfully exploited as a key step in many synthetic sequences. The catalytic loadings of $VO(acac)_2$ used (in general <10 mol %), the highly selective formation of the final compounds, and a mild oxidant such as TBHP often constitute the main advantages over classical reagents as for example *m*-chloroperoxybenzoic acid (*m*-CPBA)[4] and dioxiranes.[5] The $VO(acac)_2$/TBHP system[6] promotes other useful transformations: oxidative cyclization of bis-homoallylic alcohols to tetrahydrofuranols,[7] chemoselective dehydrogenation of acyclic and cyclic secondary alcohols to the corresponding ketones,[8] and oxidation of heteroatom-containing compounds.[9]

TABLE 1. $VO(acac)_2$/TBHP Oxidation of *o*-Propenyl Phenol 1a[a]



1a **2a**

entry	solvent	*T* (°C)	*t* (h)	yield of **2a** (%)[b]	yield of **2a** (%)[c]
1	CH_2Cl_2	rt	4	86	55
2[d]	CH_2Cl_2	rt	4	88	55
3	CH_2Cl_2	40	2	88	56
4	toluene	rt	4	68	31
5	hexane	rt	4	66	
6	CCl_4	rt	4	65	35
7	CH_3CN	rt	4	82	47

[a] Molar ratios: **1a**/$VO(acac)_2$/TBHP 1/0.02/1.2. [b] Determined by ^1H NMR analysis based on phenol **1a** employed. [c] Isolated yield after flash chromatography [d] Reaction performed in the presence of activated MS 4 Å (400 mg).

We recently reported the employment of $VO(acac)_2$/TBHP for the efficient epoxidation of a different class of compounds, the *o*-(2-alkenyl) phenols.[10] Furthermore, the highly regio- and diastereoselective oxidative cyclization to 2,3-dihydrobenzofuranols and 3-chromanols can be accomplished in one pot, using catalytic loadings of trifluoroacetic acid (TFA).[11]

In efforts to have a better insight into the reactivity of the $VO(acac)_2$/TBHP system on unsaturated phenols and to eventually enlarge its synthetic utility, we investigated the oxidation of *o*-alkenyl phenols, where the ortho C−C double bond is directly bound to the phenyl ring.

The first runs were carried out on commercially available *o*-propenyl phenol **1a**. On the basis of our previous studies, **1a** (1 mmol) was treated under mild conditions, in the presence of a catalytic amount of $VO(acac)_2$ (2 mol %) and TBHP (1.2 mmol) in dichloromethane (4 mL) under argon atmosphere at room temperature (Table 1, entry 1). The presence of molecular oxygen had to be avoided, because the $VO(acac)_2/O_2$ system has been reported to promote the oxidative coupling of phenols.[12]

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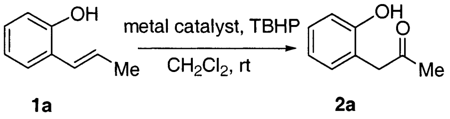
Surprisingly, instead of the expected epoxide, 1-(*o*-hydroxyphenyl)propan-2-one (**2a**) was obtained.[13] From a synthetic viewpoint this transformation has a practical value: in fact, the preparation of unmasked *o*-hydroxybenzyl ketones lacks general methods.[14] Gourges et al.[15] reported the access to free *o*-hydroxybenzyl ketones using $CrCl_2$-mediated reductive transposition of an ester acyl group in the *o*-*O*-acyl benzylic bromides. The reaction conditions had to be finely tuned to obtain the ketones in good yield, in fact to prevent the formation of side products, a slow addition of the starting bromides to $CrCl_2$ in the THF solution was required. The major drawback of this general approach to *o*-hydroxybenzyl ketones is the use of 2.5 equiv of cromium(II) salt with respect to the starting material and, in view of growing environmental concerns and sustainable chemistry, the development of a cleaner catalytic method is highly desiderable.

From ^{1}H NMR analysis of the crude reaction mixture a high conversion of **1a** to **2a** was determined (Table 1, entry 1), but after flash chromatography the product was recovered in 55% yield. This result can be ascribed to the instability of *o*-hydroxybenzyl ketones, in fact, unavoidable losses of compounds of type **2**, during the isolation process, have been previously described.[15,16] The conversion to ketone **2a** was not affected by the presence of activated MS 4 Å,[17] while a reduced reaction time was observed at 40 °C to achieve a comparable yield of **2a** (entries 2−3). In other solvents (entries 4−7) such as toluene, hexane, and CCl_4, the yield of **2a** decreased.

Other metal catalysts, commonly used in the epoxidation of alkenes, were then screened under the conditions reported in Table 1, entry 1. The results are summarized in Table 2. Both $Mo(CO)_6$ and $Ti(O\textit{i}\text{-}Pr)_4$ complexes, even after prolonged reaction time and in larger amounts (10 mol %), furnished low yields of **2a**, leaving the starting phenol **1a** unreacted. $VO(O\textit{i}\text{-}Pr)_3$, with the vanadium in the higher (V) oxidation state, is an equally efficient catalyst for the oxidation of **1a** (compare entries 3 and 4), indicating that this transformation is peculiar to oxovanadium metal complexes.

To probe the general utility of this reaction, the stable and cheap $VO(acac)_2$ was chosen as catalyst and the reactions were carried out in dichloromethane at 40 °C.

TABLE 2. Effect of Various Metal Catalysts in the Oxidation of *o*-Propenyl Phenol 1a[a]

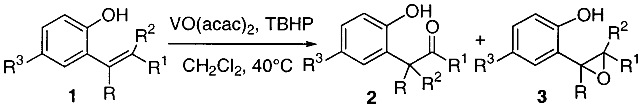


1a **2a**

entry	metal catalyst	*t* (h)	yield of **2a** (%)[b]
1	$Mo(CO)_6$ (10 mol %)	18	3
2	$Ti(O\textit{i}\text{-}Pr)_4$ (10 mol %)	18	7
3	$VO(O\textit{i}\text{-}Pr)_3$ (2 mol %)	4	83
4	$VO(acac)_2$ (2 mol %)	4	89

[a] Molar ratios: **1a**/TBHP 1/1.2. [b] Determined by ^{1}H NMR analysis based on phenol **1a** employed.

TABLE 3. $VO(acac)_2$/TBHP Oxidation of *o*-(Alkenyl) Phenols 1[a]



1 **2** **3**

entry	R	R^1	R^2	R^3	**1**	*t* (h)	yield of **2** (%)[b]	yield of **3** (%)[b]
1	H	Me	H	H	**1a**	2	56	
2	H	Bu	H	H	**1b**	5	59	
3	H	*s*-Bu	H	H	**1c**	5	64	
4	H	*t*-Bu	H	H	**1d**	4	77	
5	H	Ph	H	H	**1e**	1	50	
6[c]	H	Ph	Me	H	**1f**	1.5		82
7[c]	H	*t*-Bu	Me	H	**1g**	7		80
8[d]	C_7H_{15}	H	H	OMe	**1h**	24		

[a] Molar ratios: **1**/$VO(acac)_2$/TBHP 1/0.02/1.2. [b] Isolated yield. [c] Reaction performed at −20 °C. [d] Reaction performed at room temperature.

A variety of di- and trisubstituted C−C double bond compounds of type **1**[18] were then treated in the aforementioned conditions (Table 3). To understand if the geometry of the C−C double bond could affect the process, the reactivities of *Z* and *E* *o*-propenyl phenol **1a**, synthesized as the *Z*/*E* 55/45 mixture,[19] were compared performing the reaction at room temperature for 4 h. From ^{1}H NMR analysis of the crude reaction mixture a high conversion to **2a** (88%) was observed and the same *Z*/*E* ratio was determined in the unreacted phenol, demonstrating that the two isomers showed comparable reactivities. Longer chain alkyl substituted phenol **1b** gave a yield similar to that of model compound **1a** (entry 2). Increasing sterically demanding alkyl substituted phenols **1c**,**d** furnished higher yields of the ketones **2c**,**d** (entries 3 and 4). These results were particularly interesting even because they outlined the complementary nature of the $VO(acac)_2$/TBHP system with respect to the $CrCl_2$-mediated methodology.[15] In fact, in the last protocol, the efficiency of the transposition dramatically decreased when a sterically encumbered group was involved. As an example, the result was remarkable in entry 4, where the bulky ketone **2d** was isolated in fairly good 77% yield, while the Cr(II)-based method completely failed to give the same product. In the case of the phenyl-

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(13) The formation of ketone **2a** in low yield (10%) has been reported in the oxidation of **1a** with *m*-CPBA, see: Tinsley, S. W. *J. Org. Chem.* **1959**, *24*, 1197.

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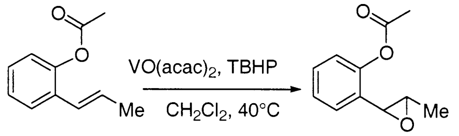
(16) When the crude reaction mixtures were purified over neutral Al_2O_3, the yields of ketones were found to be inferior with respect to the yields obtained with silica gel.

(17) The presence of molecular sieves in metal-catalyzed processes has a beneficial effect in preserving the catalyst activity. In some cases it has been reported a reaction rate enhancement ascribed to the ability of molecular sieves to accelerate ligands exchange thus generating the active catalytic complex, see: Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812.

(18) (a) Compounds **1b**−**g** were synthesized according to: Nguyen, T.; Negishi, E. *Tetrahedron Lett.* **1991**, *32*, 5903. (b) Compound **1h** was synthesized according to: Yamaguchi, M.; Hayashi, A.; Hirama, M. *J. Am. Chem. Soc.* **1995**, *117*, 1151.

(19) *Z*/*E* 55/45 mixture of **1a** was synthesized according to: Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

SCHEME 1



1i **3i**

substituted compound **1e**, an acceptable yield of the ketone was attained (entry 5). The electron-rich trisubstituted C−C double bond compounds **1f**,**g** were reacted under more controlled conditions and in this case the epoxides **3f**,**g** were isolated in very good yields (entries 6 and 7). Additional experiments were carried out on **1f**,**g**. After the generation of the epoxides **3f**,**g** at −20 °C, the reaction mixture was slowly warmed to room temperature and ^{1}H NMR analysis showed the presence of mixtures of unidentified products,[20] while no evidence of the formation of compounds of type **2** was detected. In the last entry, the terminal olefin **1h** reacted slowly at room temperature, affording a complex reaction mixture.

A reasonable mechanistic hypothesis to justify the results obtained in the oxidation of *o*-alkenyl phenols takes into account the transition metal−Lewis acid dual character[21] of the VO(acac)$_2$ complex. First, the chelation of the phenolic OH to the vanadium complex is essential for the rate enhancement in the epoxidation of **1** according to what is reported for the allylic alcohols.[3] In fact, when the reaction was performed on acetylated **1i**, after 7 h the epoxide **3i** was isolated in only 37% yield (Scheme 1).

Second, VO(acac)$_2$ plays the role of Lewis acid, promoting the rearrangement of the intermediate epoxides of compounds **1a**−**e** to ketones via selective benzylic C−O cleavage, and 1,2 hydride migration affording a single carbonyl compound. There have been a number of reports on Lewis acid-catalyzed rearrangements of epoxides to carbonyl compounds in the literature,[22] but only a few are catalytic and regioselective in nature. The constitution of the rearranged product is determined by the Lewis acid used and the migratory aptitude of the epoxide substituents. Interestingly, among them, VO(OR)Cl$_2$ catalysts have been employed in the highly regioselective rearrangement of epoxides to carbonyl compounds.[23] In this case, a greater and very fast migratory aptitude of hydrogen compared to aryl and alkyl substituents has been observed, a result that is in agreement with our observations. This behavior is different with respect to most of the Lewis acids reported for this transformation and the transition metal−Lewis acid dual character of the vanadium catalysts[21,23] might be invoked as a plausible explanation.

The hydride migration is an extremely fast process: in fact no trace of the intermediate epoxide was detected when the reaction was carried out on **1a** at −20 °C after a short reaction time (30 min), but only the presence of 10% of ketone **2a** and unreacted starting phenol was observed in the reaction mixture.[24] In the case of trisubstituted epoxides **3f**,**g** steric factors might prevent alkyl or aryl migration.[25] In the case of olefin **1h** the final rearranged product would be an aldehyde, which could suffer VO(acac)$_2$-catalyzed aldol condensation affording side products.[26]

The coordination of the phenolic OH to the metal catalyst accelerates the epoxidation of *o*-alkenyl phenols and the following rearrangement of the chelated epoxides intermediates could then be facilitated. It has to be noted that the VO(acac)$_2$/TBHP-mediated oxidation of *o*-alkenyl phenols to *o*-hydroxybenzyl ketones is analogous to the Wacker oxidation[27] of vinylarenes to form carbonyl compounds in a single step, but with the advantage of being highly regioselective.

Ketones **2** are immediate synthetic precursors of benzo[*b*]furans, which are important natural structural units[28] having interesting and several biological activities.[29] We therefore turned our attention to the possibility of developing an easy one-pot methodology based on the VO(acac)$_2$/TBHP system as a suitable alternative protocol[30] for the synthesis of benzo[*b*]furans.

On the grounds of literature reports,[15] BF$_3$·(Et$_2$O) was initially chosen as the acid catalyst to perform the intramolecular hemiketalization and dehydration of *o*-hydroxybenzyl ketones to benzo[*b*]furans (Table 4, entries 1−3). The acid (0.5 equiv) was added to the reaction mixture after the complete formation of intermediates **2**

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[20] The unidentified compounds obtained at the end of the reactions presumably derived by the phenolic OH intra- and intermolecular epoxide ring-opening.

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[23] Martínez, F.; del Campo, C.; Llama, E. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1749.

[24] Another experiment was carried out to exclude that residual acidity of silica gel, used in the workup, could be responsible for the intermediate epoxide rearrangement to ketone. Compound **1a** was reacted with VO(acac)$_2$/TBHP system, under argon atmosphere, at 0 °C in CDCl$_3$ for 2.5 h. Then, the reaction mixture was directly analyzed in an NMR tube and only ketone **2a** (40%) and unreacted **1a** were detected.

[25] Steric factors in the Lewis acid complexed epoxide can be involved preventing or favoring the alkyl or aryl migration.[22c]

[26] It has been previously reported that some acid-catalyzed rearrangements of epoxides furnished very complex reaction mixtures, whose separation afforded phenylacetaldehyde derivatives in low yields.[22d,g,h]

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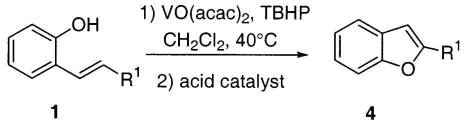
TABLE 4. One-Pot Synthesis of Benzo[*b*]furans by VO(acac)$_2$/TBHP/Acid Catalyst[a]



entry	R^1	**1**	acid catalyst	*t* (h)[c]	yield of **4** (%)[b]
1	Me	**1a**	$BF_3(Et_2O)$	2(3)	55
2	Bu	**1b**	$BF_3(Et_2O)$	3(19)	53
3	Ph	**1e**	$BF_3(Et_2O)$	1(2)	50
4	Me	**1a**	TFA[d]	2(6)	59
5	Bu	**1b**	TFA[d]	5(19)	65
6	*s*-Bu	**1c**	TFA[d]	3(19)	68
7	*t*-Bu	**1d**	TFA[d]	3(4)	82
8	Ph	**1e**	TFA[d]	1(2)	63

[a] Molar ratios: **1**/VO(acac)$_2$/TBHP 1/0.02/1.2. [b] Isolated yield. [c] Numbers in parentheses refer to reaction time in the presence of the acid catalyst. [d] 1.5 equiv of TFA was added.

was monitored by TLC. Compounds **4a**,**b**,**e** were obtained in moderate yields, but the presence of mixtures of nonpolar products was detected at the end of the reaction.

$BF_3\cdot(Et_2O)$ could competitively promote the aldol condensation of ketones **2**, so, to favor the formation of the desired products **4**, the extent of aldol condensation had to be limited by attempting more controlled reaction conditions. When employing TFA, satisfying yields of compounds **4** (entries 4–8) were indeed obtained. Better yields were achieved with increasing bulkiness of the R^1 substituent, according to the trend observed in the case of ketones **2**[31] (Table 3).

In conclusion, we have disclosed a novel reactivity of the VO(acac)$_2$/TBHP system with *o*-alkenyl phenols, which led us to set up a mild, eco-safer, practical, and general protocol for the preparation of *o*-hydroxybenzyl ketones. Because of these notable features of the reaction, this methodology competes well with that previously reported, being the one to choose for the synthesis of sterically hindered *o*-hydroxybenzyl ketones. Moreover, starting from *o*-alkenyl phenols, a useful one-pot route to benzo[*b*]furans has been easily developed based on VO(acac)$_2$/TBHP/TFA. Efforts to elucidate the scope and limitation of this oxidation system are underway.

Experimental Section

General Procedure for 2 and 3. To a stirred solution of dry CH_2Cl_2 (4 mL), under argon atmosphere, were added VO(acac)$_2$ (5.2 mg, 0.02 mmol) and **1** (1 mmol); then after 5 min TBHP (212 μL, 1.2 mmol of a 5.5 M decane solution) was added. The mixture was stirred at 40 °C for 1–7 h. At the end of the reaction, the solvent of the crude reaction mixture was partially removed in vacuo and the concentrated crude mixture was filtered through a small pad of silica gel before ^{1}H NMR analysis. Then the reaction mixture was purified by flash chromatography eluting with petrol–Et_2O mixtures from 80:20 to 70:30.

General Procedure for 4. To a stirred solution of dry CH_2Cl_2 (4 mL), under argon atmosphere, were added VO(acac)$_2$ (5.2 mg, 0.02 mmol) and **1** (1 mmol); then after 5 min TBHP (212 μL, 1.2 mmol of a 5.5 M decane solution) was added. The mixture was stirred at 40 °C until the complete formation of **2** (TLC analysis). Then, TFA (112 μL, 1.5 mmol) was added and the reaction mixture was stirred for 2–19 h. At the end of the reaction, the solvent was evaporated under reduced pressure and the crude mixture was purified by flash chromatography eluting with petrol–Et_2O (99:1).

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Supporting Information Available: Experimental procedures and characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) All the yields of benzo[*b*]furans are higher than the yields of the corresponding ketones **2** in Table 3; these results confirm the silica gel induced decomposition of **2** during the purification process.