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Microwave-Assisted Meyer–Schuster Rearrangement of Propargylic Alcohols Catalyzed by the Oxovanadate Complex $[V(O)Cl(OEt)_2]$

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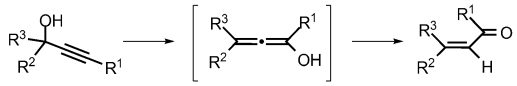
A general and efficient procedure for the selective Meyer–Schuster isomerization of both, terminal and internal alkynols, has been developed by using catalytic amounts of the readily accessible oxovanadium(V) complex $[V(O)Cl(OEt)_2]$. Reactions proceeded smoothly in toluene at 80 °C under microwave irradiation to provide the corresponding α,β-unsaturated carbonyl compounds in excellent yields and short times without the assistance of any additive.

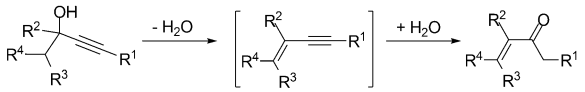
Introduction

α,β-Unsaturated carbonyl compounds are useful building blocks in organic synthesis, advanced intermediates in the manufacture of aromas and fragrances, and key structural units in a large number of biologically active natural products.[1] Such species are usually obtained by using aldol- or Knoevenagel-type condensation reactions and by using Wittig and Horner–Wadsworth–Emmons olefination processes.[1,2] However, in addition to their low atom economy,[3] these classical methods generally require strongly basic media and, therefore, functional group compatibility and selectivity issues can be problematic. An alternative method of synthesis is the isomerization of propargylic alcohols through a formal 1,3-shift of the hydroxyl moiety, which is known as the Meyer–Schuster rearrangement (Scheme 1).[4]



Scheme 1. The Meyer–Schuster rearrangement of propargylic alcohols.

However, despite the accessibility of the starting materials, which can be easily generated by simple addition of metallated alkynes to aldehydes or ketones, and its complete atom economy, the Meyer–Schuster rearrangement has remained largely forgotten. This is attributable to the low selectivities often shown by the traditional protocols, which are based on the use of strong Brønsted acids under harsh reaction conditions.[5] In particular, starting from substrates able to undergo a competitive Rupe-type rearrangement (Scheme 2),[6] non-regioselective transformations are usually observed.



Scheme 2. The Rupe rearrangement of propargylic alcohols.

With the gradual emergence of new synthetic approaches based on the use of metal catalysts, more selective and efficient under milder reaction conditions,[7,8] the Meyer–Schuster rearrangement has begun to play a more prominent role within the toolbox of synthetic organic chemists. In particular, remarkable results have been recently reported by several groups in tandem processes that involved the combination of this isomerization reaction with condensation,[9] cyclocondensation,[10] asymmetric hydrosilylation,[11] Nazarov-type electrocyclization,[12] Michael-type addition,[13] oxirane ring-opening,[14] and allylic alkylation[15] reactions, all of them allowing rapid access to elaborated structures from readily available propargylic alcohols.[16] Clearly, the inclusion of this textbook transformation in future research programs is highly dependent on the availability of simple and effective catalytic systems, an area of research open for many opportunities of new discoveries.

Metal oxides and oxo complexes are among the most popular catalysts employed for the isomerization of alkynols because they show a remarkable selectivity toward the Meyer–Schuster as opposed to the Rupe reaction.[7] This selectivity stems from the mechanism of action of these catalysts, which

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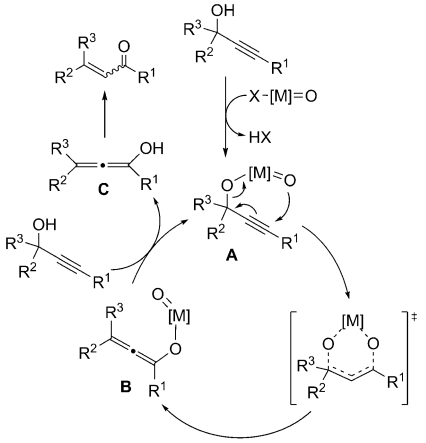
involves, as the key step, a [3,3]-sigmatropic rearrangement of a metal-oxo-propargyloxo intermediate **A**, initially generated by transesterification of the metallic precursor with the propargylic alcohol (Scheme 3).[17,18] Subsequent alkoxide exchange in the thus generated allenyloxo species **B** liberates the allenol **C**, which readily tautomerizes into the desired α,β-unsaturated carbonyl compound and regenerates **A**.[19]



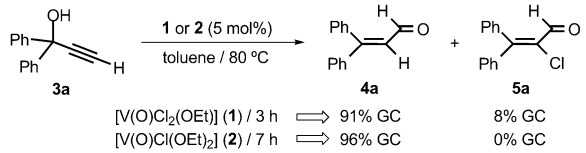
Scheme 3. General mechanism for the Meyer–Schuster rearrangement catalyzed by metal (M)-oxo species. X = halide, alkoxide.

In agreement with the well-known ability of oxovanadium(V) complexes to catalyze oxygen transfer reactions,[20] several orthovanadate derivatives of the general composition $[V(O)(OR)_3]$ (R = alkyl, aryl, or silanyl group) were proven to act as promoters of Meyer–Schuster-type rearrangements.[21] However, these complexes usually operate under high temperature regimes (140–160 °C) or in the presence of acidic cocatalysts, which seriously limits their synthetic applications.[22]

Recently, some of us developed a simple, clean, selective, and straightforward method for the synthesis of chlorinated oxo-alkoxide complexes $[V(O)(Cl)_{3-x}(OR)_x]$ ($x = 1$ or 2; R = alkyl group) by the treatment of commercially available vanadyl chloride $[V(O)Cl_3]$ with varying excesses of silicon ethers ($ROSiMe_3$) under mild conditions.[23] Easy access to these complexes on the multigram scale, along with the ability of their nonchlorinated $[V(O)(OR)_3]$ counterparts to promote Meyer–Schuster rearrangements, prompted us to study the catalytic behavior of these species. We reasoned that the higher reactivity of the V–Cl versus V–OR bonds could facilitate the initial transesterification step (formation of intermediate **A** in Scheme 3), thus improving the effectiveness of this type of oxo catalysts. This assumption was correct, and a new procedure for the selective Meyer–Schuster isomerization of both terminal and internal alkynols could be developed by using $[V(O)Cl(OEt)_2]$ as the catalyst. Thus, compared to the $[V(O)(OR)_3]$-based systems described previously, the complex $[V(O)Cl(OEt)_2]$ could operate under remarkably milder reaction conditions (80 °C) without the assistance of any additive.

Results and Discussion

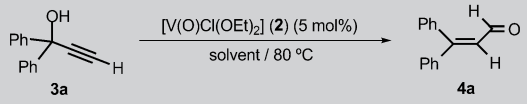
To prove the catalytic potential of the oxovanadium(V) compounds $[V(O)(Cl)_{3-x}(OR)_x]$ ($x = 1$ or 2), the isomerization of commercially available 1,1-diphenyl-2-propyn-1-ol (**3a**) into 3,3-diphenylpropenal (**4a**) was first explored by using complexes $[V(O)Cl_2(OEt)]$ (**1**) and $[V(O)Cl(OEt)_2]$ (**2**) as model catalysts (Scheme 4). Thus, by performing the catalytic reactions in toluene (1 M solution of **3a**) at 80 °C, both complexes were able to generate the desired enal **4a** in high GC yields (91–96%) after only 3–7 h of heating. Although a faster reaction was observed with the dichloride derivative $[V(O)Cl_2(OEt)]$ (**1**), the process was not completely selective because, in addition to **4a**, minor amounts (8% by GC) of a by-product were also formed. After chromatographic purification of the mixture, this by-product could be separated and identified spectroscopically as the known 2-chloro-3,3-diphenylacrylaldehyde (**5a**), which resulted formally from the vinylic chlorination of **4a**.[24] Interestingly, such a chlorination process was not observed when the monochloride derivative $[V(O)Cl(OEt)_2]$ (**2**) was used as catalyst, which reveals the key role played by the number of chlorine atoms attached to vanadium in the chemoselectivity of this catalytic reaction.



Scheme 4. The behavior of 1,1-diphenyl-2-propyn-1-ol toward the complexes $[V(O)Cl_2(OEt)]$ (**1**) and $[V(O)Cl(OEt)_2]$ (**2**).

The catalytic behavior of the most selective catalyst $[V(O)Cl(OEt)_2]$ (**2**) was then explored in different solvents (acetonitrile, acetone, and THF), but, as shown in Table 1, the use of these polar media did not allow for an improvement of the activity

Table 1. Isomerization of 1,1-diphenyl-2-propyn-1-ol (**3a**) into 3,3-diphenylpropenal (**4a**) catalyzed by $[V(O)Cl(OEt)_2]$ (**2**) in different solvents.[a]



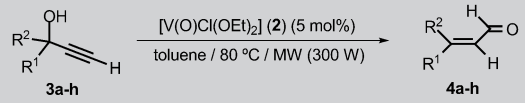
Entry	Solvent	*t* [h]	Yield [%][b]
1	toluene	7	96
2	acetonitrile	24	94
3	acetone	24	42
4	tetrahydrofuran	24	96
5[c]	toluene	0.5	97

[a] Reactions were performed in a sealed tube under N_2 atmosphere at 80 °C. 1,1-Diphenyl-2-propyn-1-ol (**3a**) was used (1 mmol, 1.0 M solution). Ratio [substrate]/[V] = 100:5. [b] Yield of 3,3-diphenylpropenal (**4a**) determined by using GC. [c] Reaction was performed under N_2 atmosphere in a CEM Discover S-Class microwave synthesizer at 80 °C through moderation of the initial power (300 W).

of **2**. Thus, although the selective formation of enal **4a** was observed in all cases, a longer reaction time (24 h) was required to attain similar or even poorer conversions (entries 2–4 versus entry 1).

It is well recognized that the use of microwave (MW) irradiation represents a convenient alternative to conventional thermal heating in organic synthesis because a more effective energy transfer to the system occurs, which thus shortens the reaction times considerably and improves, in many cases, the product yields.[25] Accordingly, the isomerization of **3a** into **4a** promoted by $[V(O)Cl(OEt)_2]$ (**2**) proceeds almost quantitatively in only 30 min when MW irradiation (300 W) is used as the heating source (80 °C; entry 1 in Table 2).[26] Remarkably, the effectiveness shown by **2** under these conditions surpasses by far those reported previously for the classical oxovanadium(V) catalysts $[V(O)(OR)_3]$[21] and that of the highly reactive oxorhenium(V) derivative $[Re(O)Cl_3(OPPh_3)(SMe_2)]$ described by Vidari and coworkers.[16a] Isomerization of **3a** by using the latter (5 mol% loading) leads to 3,3-diphenylpropenal (**4a**) in 96% yield only after 20 h of heating at 80 °C.[16a]

Table 2. Isomerization of tertiary propargylic alcohols **3a–h** into enals **4a–h** catalyzed by $[V(O)Cl(OEt)_2]$ (**2**).[a]



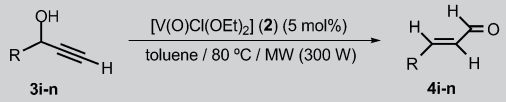
3a-h 4a-h

Entry	Substrate **3**	*t* [h]	Yield of **4** [%][b]
1	$R^1=R^2=$Ph (**3a**)	0.5	**4a**; 97 (93)
2	$R^1=R^2=$2,2′-C_6H_4–C_6H_4 (**3b**)	1	**4b**; 98 (91)
3	$R^1=R^2=$2,2′-C_6H_4–CH=CH–C_6H_4 (**3c**)	0.5	**4c**; 99 (95)
4	$R^1=R^2=$4-C_6H_4F (**3d**)	2.5	**4d**; 98 (93)
5	$R^1=R^2=$4-C_6H_4Cl (**3e**)	1	**4e**; 96 (93)
6	$R^1=R^2=$4-C_6H_4OMe (**3f**)	0.25	**4f**; 97 (92)
7	$R^1=R^2=$4-C_6H_4Me (**3g**)	0.33	**4g**; 98 (94)
8	$R^1=$Me; $R^2=$Ph (**3h**)	1	**4h**; 98 (93)[c]

[a] Reactions were performed under N_2 atmosphere in a CEM Discover S-Class microwave synthesizer at 80 °C through moderation of the initial power (300 W). The corresponding alkynol was used (1 mmol, 1.0 M solution in toluene). Ratio [substrate]/[V] = 100:5. [b] Determined by using GC. Isolated yields after chromatographic workup are given in parentheses. [c] A mixture of *E* and *Z* isomers in an approximately 3:2 ratio is formed.

By using these optimized reaction conditions, complex $[V(O)(Cl)(OEt)_2]$ (**2**) efficiently catalyzed the selective isomerization of a large number of other propargylic alcohols, which proves the wide scope and synthetic utility of this catalytic transformation. Thus, as observed for 1,1-diphenyl-2-propyn-1-ol (entry 1 in Table 2), other tertiary alkynols **3b–h** underwent fast (0.25–2.5 h) and selective isomerization into the corresponding enals **4b–h**, which could be isolated after appropriate chromatographic workup in excellent yields (91–95%; entries 2–8 in Table 2). An influence of the electronic properties of the aryl rings on the reaction rates was observed. Alkynols with electron-withdrawing groups showed less reactivity (entries 4 and 5) as compared to the substrates with electron-donating substituents (entries 6 and 7).

Table 3. Isomerization of secondary propargylic alcohols **3i–n** into enals **4i–n** catalyzed by $[V(O)Cl(OEt)_2]$ (**2**).[a]



3i-n 4i-n

Entry	Substrate **3**	*t* [h]	Yield of **4** [%][b]
1	R = Ph (**3i**)	5	**4i**; 97 (92)
2	R = 2-naphthyl (**3j**)	8	**4j**; 97 (91)
3	R = 2-C_6H_4OMe (**3k**)	4	**4k**; 95 (87)
4	R = 4-C_6H_4Cl (**3l**)	7	**4l**; 95 (89)
5	R = 4-C_6H_4SMe (**3m**)	6	**4m**; 97 (91)
6	R = 2-thienyl (**3n**)	4	**4n**; 95 (92)

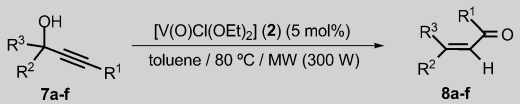
[a] Reactions were performed under N_2 atmosphere in a CEM Discover S-Class microwave synthesizer at 80 °C through moderation of the initial power (300 W). The corresponding alkynol was used (1 mmol; 1.0 M solution in toluene). Ratio [substrate]/[V] = 100:5. [b] Determined by using GC. Isolated yields after chromatographic workup are given in parentheses.

The behavior of complex **2** toward 2-phenyl-3-butyn-2-ol (**3h**, entry 8), a propargylic alcohol bearing a C–H bond in the β position with respect to the alcohol group in which the isomerization process can proceed through the competitive Rupe-type rearrangement, was also explored. An exclusive formation of the α,β-unsaturated enal **4h**, as a mixture of the corresponding *E* and *Z* stereoisomers in an approximately 3:2 ratio, was observed.[27] In an attempt to improve the stereoselectivity of this reaction, we increased the steric congestion on the vanadium center by replacing one of the ethoxy groups (OEt) by the bulkier adamantoxy one (OAd). This was easily achieved by adding a stoichiometric amount of 1-adamantanol to a dichloromethane solution of complex $[V(O)Cl(OEt)_2]$ (**2**). The reaction yielded the mixed alkoxy vanadate complex [V(O)Cl(OEt)(OAd)] (**6**) in good yield (97%) as an orange oil (synthetic details and characterization data are given in the Experimental Section). Unfortunately, the use of **6** as catalyst (5 mol%) resulted in the same mixture of *E/Z* isomers in 98% GC yield after 1.5 h of MW irradiation. This clearly indicates that the stereochemistry of the C=C bond is fixed out of the coordination sphere of the metal.

Secondary terminal alkynols (Table 3) can also be efficiently and selectively isomerized into the corresponding enals by using $[V(O)(Cl)(OEt)_2]$ (**2**). Again, reactions proceeded to completion in the absence of any cocatalyst. However, in these cases, longer reaction times were required compared to the aforementioned tertiary propargylic alcohols (4–8 h vs. 0.25–2.5 h). Interestingly, in contrast to **4h**, the resulting enals **4i–n** were now exclusively obtained as the thermodynamically more stable *E* isomers, regardless of the electronic properties of the aromatic substituents present in the molecule.[28]

As shown in Table 4, the effectiveness of complex **2** is not restricted to propargylic alcohols bearing a terminal C≡C bond: the internal ones in **7a–f** are also efficiently transformed into the corresponding enones **8a–f** under identical reaction conditions (91–95% isolated yields after 0.5–6.5 h of MW irradiation). Both tertiary (**7a–b**; entries 1 and 2) and secondary (**7c–f**; entries 3–5) alcohols were tolerated, the latter leading

Table 4. Isomerization of internal propargylic alcohols **7a–f** into enones **8a–f** catalyzed by $[V(O)Cl(OEt)_2]$ (**2**).[a]



7a-f 8a-f

Entry	Substrate **7**	*t* [h]	Yield of **8** [%][b]
1	$R^1=R^2=R^3=$Ph (**7a**)	0.5	**8a**; 99 (95)
2	$R^1=CF_3$; $R^2=R^3=$Ph (**7b**)	1	**8b**; 96 (92)
3	$R^1=$Me; $R^2=$Ph; $R^3=$H (**7c**)	6	**8c**; 96 (91)[c]
4	$R^1=$Me; $R^2=$4-C_6H_4OMe; $R^3=$H (**7d**)	3.5	**8d**; 97 (94)[c]
5	$R^1=$Me; $R^2=$4-C_6H_4SMe; $R^3=$H (**7e**)	6.5	**8e**; 96 (93)[c]
6	$R^1=$Ph; $R^2=$Ph; $R^3=$H (**7f**)	0.5	**8f**; 98 (94)[c]

[a] Reactions were performed under N_2 atmosphere in a CEM Discover S-Class microwave synthesizer at 80 °C through moderation of the initial power (300 W). The corresponding alkynol was used (1 mmol, 1.0 M solution in toluene). Ratio [substrate]/[V] = 100:5. [b] Determined by using GC. Isolated yields after chromatographic workup are given in parentheses. [c] *E* isomers were formed exclusively.

to enones **8c–f** with complete *E* stereoselectivity. The clean isomerization of the CF_3-containing propargylic alcohol **7b** into enone **8b** (entry 2) merits to be highlighted because α,β-unsaturated trifluoromethyl ketones $R^1R^2C{=}C(R^3)C(=O)CF_3$ are important building blocks in organic syntheses. The enhanced reactivity of these derivatives, as compared to their nonfluorinated counterparts, has been widely exploited in a large number of processes, including Diels–Alder cycloadditions and Michael-type additions.[29] As far as we are aware, transformation of **7b** into **8b** represents the first example of a Meyer–Schuster rearrangement of propargylic alcohols with a trifluoromethyl group at the distal position of the C≡C triple bond,[30] which thus opens a new route of access to these relevant enones.[31]

Finally, the limitations of this new methodology are: 1) the scope of this transformation is limited to benzylic alcohols, and 2) the use of primary propargylic alcohols $RC{\equiv}CCH_2OH$, which gives rise to intractable polymeric materials under standard reaction conditions.[32]

Conclusions

A novel procedure for the Meyer–Schuster rearrangement of propargylic alcohols has been developed by using the oxovanadium(V) complex $[V(O)Cl(OEt)_2]$, a readily accessible species that can be generated on the multigram scale from commercially available vanadyl chloride $[V(O)Cl_3]$ and ethoxytrimethylsilane ($EtOSiMe_3$) in a single step. Under MW irradiation, this compound was able to isomerize both terminal and internal propargylic alcohols into the corresponding α,β-unsaturated carbonyl compounds, which can be obtained 1) under milder conditions (80 °C) compared to the previously reported examples using orthovanadate derivatives $[V(O)(OR)_3]$, 2) in excellent yields, 3) in most cases on a time-scale reaction of minutes, and 4) under neutral conditions assisted by MW irradiation. This catalyst was also proven to promote chemoselective and regioselective transformations, which lead in all cases to the most stable *E* isomers when secondary propargylic alcohols are used as substrates. To the best of our knowledge, complex $[V(O)Cl(OEt)_2]$, along with the oxorhenium(V) derivative $[Re(O)Cl_3(OPPh_3)(SMe_2)]$ described by Vidari and coworkers,[16a] is the most efficient oxo catalyst reported to date in the literature for this relevant transformation. We are confident that this simple methodology can be of interest to a wide range of synthetic organic chemists, who could use it in future research programs.

Experimental Section

General methods

Synthetic procedures were performed under an atmosphere of dry nitrogen. Solvents were dried by using standard methods and distilled under nitrogen before use. All reagents were purchased from commercial suppliers and used without further purification, with the exception of complexes $[V(O)Cl_2(OEt)]$ (**1**) and $[V(O)Cl(OEt)_2]$ (**2**),[23] the terminal propargylic alcohols **3b–g** and **3j–n** (Tables 2 and 3),[33] and the internal propargylic alcohols **7b–e** (Table 4),[28a,30,34] which were prepared by following the methods reported in the literature. Flash chromatography was performed by using Merck silica gel 60 (230–400 mesh).

General procedure for the catalytic Meyer–Schuster rearrangements using $[V(O)Cl(OEt)_2]$ (2)

Under nitrogen atmosphere, a pressure-resistant septum-sealed glass vial was charged with the corresponding propargylic alcohol (1 mmol), $[V(O)Cl(OEt)_2]$ (0.010 g, 5 mol%), a magnetic stirring bar, and toluene (1 mL). The vial was then placed inside the cavity of a CEM Discover S-Class microwave synthesizer, and the power was held at 300 W until the desired temperature (80 °C) was reached. Microwave power was automatically regulated for the remainder of the experiment to maintain the temperature (monitored by a built-in infrared sensor). The course of the reaction was monitored by performing regular sampling and analysis by using GC. After completion of the reaction (Tables 2–4), the vial was cooled and the crude of the reaction was purified by using flash chromatography over silica gel using ethyl acetate/hexane (1:10) as eluent. The identity of the resulting α,β-unsaturated carbonyl compounds was assessed by comparison of their ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data (copies of the spectra are included in the Supporting Information) with those reported in the literature and by their fragmentation in GC–MS.

Synthesis of complex [V(O)Cl(OEt)(OAd)] (6)

Under a nitrogen atmosphere, a solution of 1-adamantanol (0.79 g, 5.20 mmol) in dichloromethane (10 mL) was slowly added to a solution of $[V(O)Cl(OEt)_2]$ (**2**) (1.00 g, 5.20 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 2 h at room temperature to obtain a light orange solution. The solvent was then removed under vacuum to give compound **6** as an orange oil. Yield: 1.50 g (97%); ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 1.57$ (t, $J = 7$ Hz, 3H, OCH_2CH_3), 1.70 (m, 6H, $OC(CH_2)_3(CH)_3(CH_2)_3$), 2.08 (m, 6H, $OC(CH_2)_3(CH)_3(CH_2)_3$), 2.29 (br s, 3H, $OC(CH_2)_3(CH)_3(CH_2)_3$), 5.33 ppm (q, $J = 7$ Hz, 2H, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 25 °C): $\delta =$ 19.12 (OCH_2CH_3), 31.55 ($OC(CH_2)_3(CH)_3(CH_2)_3$), 35.98 ($OC(CH_2)_3(CH)_3(CH_2)_3$), 45.04 ($OC(CH_2)_3(CH)_3(CH_2)_3$), 82.86 (OCH_2CH_3), 91.67 ppm ($OC(CH_2)_3(CH)_3(CH_2)_3$); elemental analysis calcd (%) for $C_{12}H_{20}ClO_3V$ (298.7 g mol^{-1}): C 48.26, H 6.75; found: C 48.50, H 2.85.

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