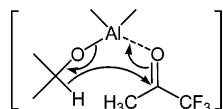# Oppenauer Oxidation of Secondary Alcohols with 1,1,1-Trifluoroacetone as Hydride Acceptor

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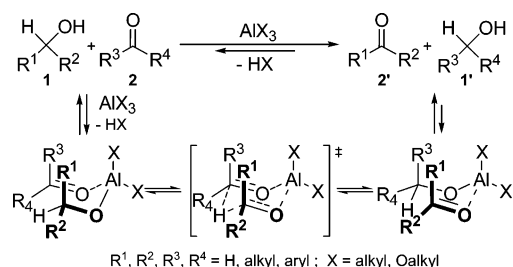
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1,1,1-Trifluoroacetone (**2a**) reacts as a hydride-acceptor in the Oppenauer oxidation of secondary alcohols (**1**) in the presence of diethylethoxyaluminum. The oxidant allows for selective oxidation of secondary alcohols in the presence of primary alcohols.

The Oppenauer oxidation of alcohols (**1**) is a highly selective reaction that can be performed with simple organic molecules as oxidants and easily accessible and inexpensive metal alkoxides as catalysts under mild conditions.[1] This reaction is performed with Lewis acids derived from aluminum, magnesium, or boron, either in solution or on solid support, and employs aldehydes as suitable oxidants. The research for more efficient catalysts and reaction conditions allowed the synthetic applications of this oxidation method, which can presently be efficiently applied at preparative scale, to be extended.[2]

It is generally accepted[1] that Oppenauer oxidation proceeds via a complex in which both the hydride-acceptor carbonyl group and the alcohol (**1**) are bound to the metal ion (Scheme 1). The carbonyl group, which is activated upon coordination with the metal ion, initiates the hydride abstraction process from the alkoxide ligand via a concerted six-membered transition state. The reaction is reversible and the equilibrium position is determined by the reduction potentials of the carbonyl compounds involved.[1] Carbonyl compounds with low reduction

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SCHEME 1. Oppenauer Oxidation Reaction Mechanism

R^1, R^2, R^3, R^4 = H, alkyl, aryl ; X = alkyl, Oalkyl

potentials are suitable oxidants in Oppenauer oxidations and most of the recently described procedures use aromatic and aliphatic aldehydes as hydride acceptors (Scheme 1, R^3 = H, R^4 = alkyl, aryl).

On the other hand, it is known that introduction of fluorine substituents in ketones (**2**) enhances the electrophilic reactivity of the carbonyl group, reduces their Lewis basicity, and increases the stability of their addition products.[3] Thus, the chemical reactivity of perfluorinated ketones significantly differs from that of their hydrogenated counterparts. For instance, it has been described[3] that hexafluoroacetone reacts with tertiary amines via hydride abstraction from the carbon atom at the α-position to result in the corresponding iminium salt and 1,1,1,2,2,2-hexafluoro-2-propanol. However, this enhanced hydride-acceptor ability of fluorinated ketones has not yet been tested in the Oppenauer reaction.

We report herein that 1,1,1-trifluoroacetone (**2a**) is a suitable reagent to perform the oxidation of secondary alcohols (**1**) to ketones (**2**) in the presence of diethylethoxyaluminium under mild conditions (eq 1). Moreover, the oxidation is selective and

R, R' = alkyl, aryl
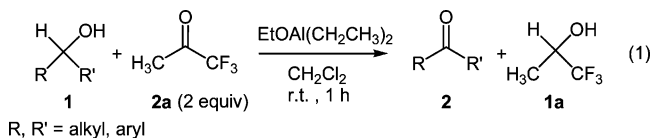
primary alcohols remain unchanged under the reaction conditions. 1,1,1-Trifluoroacetone (**2a**) and 1,1,1-trifluoro-2-propanol (**1a**) are volatile compounds removed from the reaction mixture by evaporation thus simplifying the workup and isolation of the products.

Reactions were carried out by adding 1,1,1-trifluoroacetone (**2a**) to a mixture of the starting alcohol (**1**) and diethylethoxyaluminum in dichloromethane (molar ratio **1**:**2a**:(CH₃CH₂)₂-AlOEt 1:2:0.3) (eq 1). The mixture was allowed to react at room temperature in a tightly closed flask. The aluminum alkoxides were hydrolyzed by treatment with the stoichiometric amount of water, the mixture was dried with anhydrous sodium sulfate, and the resulting ketones were isolated by vacuum evaporation of solvent. The results are shown in Table 1.

Oxidations take place efficiently for secondary alcohols **1** in the presence of C=C double bonds (entries 1−7, Table 1). Primary allylic alcohols (entry 9, Table 1) and primary aliphatic alcohols do not react efficiently under these reaction conditions. Reactions performed at 40 °C in a sealed vial led to slower

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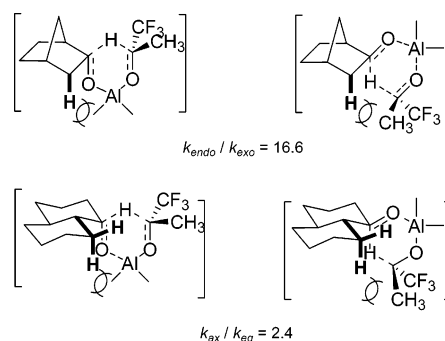
TABLE 1. Oppenauer Oxidation of Alcohols 1 with 1,1,1-Trifluoroacetone 2a[a]

Run	Substrate[b] (1)	t (h)	Product[c]
1	(1b)	8	(2b)
2	(1c)	8	(2c)
3	(1d)	7	(2d)
4[d]	(1e)	(exo-) 3 (endo-) 2	(2e)
5[d]	(1f)	1	(2f)
6[d]	(1g)	6	(2g)
7	(1h)	20	(2h)
8[e]	(1i)	18	(2i)
9[f]	(1j)	24	(2j)
10[g]	(1k)	20	(2k)

[a] Reactions performed in dichloromethane/toluene at rt with initial molar ratio **1**:**2a**:Et₂AlOEt 1:2:0.3. [b] Substrate conversion was complete for all cases except where noted. [c] Isolated product yield was >99% in all cases except where noted. [d] Initial molar ratio **1**:**2a**:Et₂AlOEt 1:2:0.1. [e] Substrate conversion was 26%. [f] Initial molar ratio **1j**:**2a**:Et₂AlOEt 1:2:0.5, substrate conversion 46%. [g] Initial molar ratio **1k**:**2a**:Et₂AlOEt 1:5:0.3, substrate conversion >99%.

FIGURE 1. Transition states for the oxidation of *exo* and *endo*-norbornanol (**1e**) and *axial* and *equatorial trans*-1-decalol (**1i**).

The reactions are more efficient for cyclic, polycyclic, and rigid substrates than for their alycyclic counterparts (entries 1 and 7, Table 1). This result indicates that for linear substrates it is difficult to achieve the highly ordered structure required for the hydride transfer process to take place.

When 1,1,1-trifluoroacetone (**2a**) is the hydride acceptor either a methyl or trifluoromethyl substituent is placed in the pseudo-axial position in the transition state structure, with a significant steric interaction with one of the substituents of the secondary alcohol (Scheme 1). A comparison between the reactivity of 1-decalol (**1i**) and the structurally related alcohols cyclohexanol (**1b**), 2-adamantanol (**1f**), or norbornanol (**1e**) shows the effect of the steric hindrance on the oxidation rate.

The relative reaction rates found for the oxidation of *endo*- and *exo*-norbornanol (**1e**) ($k_{endo}/k_{exo} = 16.6$) and 1-decalol (**1i**) ($k_{ax}/k_{eq} = 2.4$) can be attributed to the differences in steric crowding at the corresponding diastereomeric transition states (Figure 1) and also to the release of torsional strain in the alcohol cyclic systems on going from an sp³ to an sp² carbon atom in the ketone.

Primary alcohols were unreactive under our standard reaction conditions indicating that in these conditions the reduction potential of 1,1,1-trifluoroacetone (**2a**) ($E^o_{red} = -1.3$ V)[4] lies between those of simple dialkyl ketones and aliphatic aldehydes. This characteristic of 1,1,1-trifluoroacetone prompted us to attempt the selective oxidation of secondary alcohols in the presence of a primary alcohol. Effectively, the reaction of an equimolar mixture of cyclohexanol (**1b**) and *n*-heptanol (**1l**) with 2 equiv of 1,1,1-trifluoroacetone (**2a**) and 30% diethylethoxy-aluminum in dichloromethane/toluene at room temperature allowed for the complete conversion of **1b**, while the primary alcohol remained unchanged. The competition reaction performed between cyclohexanol (**1b**) and *trans*-2-hexenol (**1j**) led to 73% conversion of **1b** and 27% conversion of **1j**. This indicates that the unsaturated aldehyde **2j** has a reduction potential more negative than the aliphatic aldehyde **2l**. This enables the allylic alcohol **1j** to compete more efficiently with cyclohexanol (**1b**) in the hydride transfer process to 1,1,1-trifluoroacetone. On the other hand, the oxidation of *endo*-2-norbornanol (**1e**), which is more reactive than cyclohexanol (**1b**) (entries 1 and 4, Table 1), can be performed selectively in the presence of an equimolar amount of benzyl alcohol under the same reaction conditions (eq 2). Therefore, for the oxidation of

reactions and lower conversion values. This observation was attributed to the high vapor pressure of 1,1,1-trifluoroacetone (**2a**) (13.2 psi at 20 °C), which favors the oxidant to escape to the vapor phase and results in a lower availability in solution. The data show that, despite the electron-withdrawing effect of the trifluoromethyl group, 1,1,1-trifluoroacetone is basic enough to coordinate with the aluminum Lewis acid (Scheme 1). On the other hand, the oxidation of 2-adamantanol (**1f**) and benzyl alcohol with acetone under our reaction conditions led to only 4% conversion of the substrates after 15 h, indicating that the fluorine substituents significantly enhance the hydride abstraction ability of the carbonyl group.

The corresponding magnesium alkoxides led to lower substrate conversions. For instance, the reaction of cyclohexanol (**1b**) with 1.1 equiv of methylmagnesium bromide in toluene/THF followed by treatment with 1.5 equiv of 1,1,1-trifluoroacetone at room temperature for 5 h allowed a 63% yield of the corresponding ketone (**2b**) to be obtained. The reaction with magnesium alkoxides derived from other alcohols led to complex mixtures of undefined materials with partial recovery of the reactants.

(4) Adam, W.; Asensio, G.; Curci, R.; González-Núñez, M. E.; Mello, R. *J. Am. Chem. Soc.* **1992**, *114*, 8345−8349.

(2)

conv. 100%

SCHEME 2. Oxidation of 1,5-Hexanediol with 1,1,1-Trifluoroacetone and (CH₃CH₂)₂AlOEt
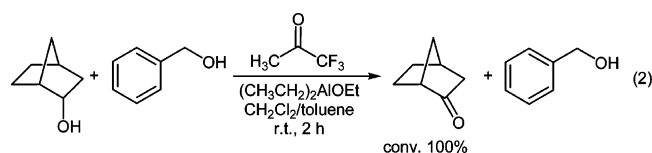

a secondary alcohol with 1,1,1-trifluoroacetone (**2a**) to be selective in the presence of a primary alcohol, it is necessary that the reduction potentials of the corresponding carbonyl compounds are different enough to allow for a favorable equilibrium under our reaction conditions.

However, the presence of both primary and secondary hydroxy functionalities in the same molecule can lead to alternative oxidation pathways. Thus, the selective oxidation of the secondary alcohol moiety in 1,4-hexanediol with 1,1,1-trifluoroacetone (**2a**) and diethylethoxyaluminum failed. The reaction was extremely slow and led to a mixture of 5-methyl-2-oxotetrahydropirane and 2-ethoxy-5-methyltetrahydropirane as the main products (Scheme 2) by oxidation of the primary alcohol of the substrate. Perhaps, as the hydride transfer process in the Oppenauer oxidation is reversible, the reaction is channeled toward the corresponding lactone through the formation of an intermediate aldehyde followed by the highly favored oxidation of the cyclic hemiacetal (Scheme 2). On the other hand, complexation of 1,4-hexanediol with aluminum and/or formation of a cyclic acetal with 1,1,1-trifluoroacetone (**2a**) might hinder the hydride-transfer process from the secondary alcohol.

Then it seems that the selective oxidation of the secondary alcohol moiety in diols is not possible if both alcohols can simultaneously coordinate the metal ion. Effectively, the oxidation of 2-[4-(1-hydroxyethyl)phenoxy]ethanol (**1k**) with 1,1,1-trifluoroacetone (**2a**) in the presence of diethylethoxyaluminium (initial molar ratio 1:5:0.3) for 10 h led exclusively to the oxidation of the secondary benzylic hydroxy group (entry 10, Table 1).

To summarize, we have described the Oppenauer oxidation of secondary alcohols (**1**) promoted by 1,1,1-trifluoroacetone (**2a**) in the presence of diethylethoxyaluminum. This protocol enables the selective oxidation of secondary alcohols in the presence of primary alcohols and, with some restrictions, the selective oxidation of the secondary alcohol moiety in mixed primary/secondary diols.
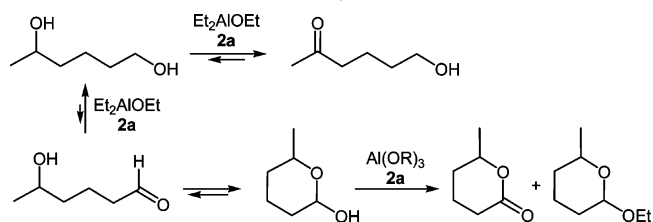
Experimental Section

Oxidation of 2-Adamantanol (1f). General Procedure. A stirred solution of 0.24 g of 2-adamantanol (**1f**) (1.6 mmol) in 10 mL of dichloromethane was treated with 0.1 mL of a 1.6 M solution of diethylethoxyaluminum in toluene (0.1 equiv) at room temperature. After 5 min, 0.3 mL of 1,1,1-trifluoroacetone (3.2 mmol) was added at once. Commercial 1,1,1-trifluoroacetone was used without further purification. The flask was tightly closed and allowed to stand at room temperature for 1 h. The reaction mixture was treated for 15 min with 0.25 mL of water and then with MgSO₄. The solution was filtered and the solvent was removed under vacuum to yield 0.24 g of 2-adamantanone (**2f**) as a white solid.

Competition Experiments. A stirred solution of 50 mg of cyclohexanol (**1b**) (0.5 mmol) and 58 mg of *n*-heptanol (**1l**) (0.5 mmol) in 3 mL of dichloromethane was treated with 0.188 mL of a 1.6 M solution of diethylethoxyaluminum in toluene (0.3 mmol) at room temperature. After 2 min, 0.18 mL of commercial 1,1,1-trifluoroacetone (2 mmol) was added at once. The flask was tightly closed and allowed to stand at room temperature. The reaction advance was monitored by treating 0.1 mL samples diluted with 0.5 mL of dichloromethane for 5 min with 3 *μ*L of water and then dried with MgSO₄.

Supporting Information Available: GC-MS spectra of the crude reaction mixtures. This material is available free of charge via the Internet at http://pubs.acs.org.

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