Tetrahedron Letters 53 (2012) 890–892

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ytterbium triflate catalysed Meerwein–Ponndorf–Verley (MPV) reduction

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ARTICLE INFO

Article history:
Received 11 October 2011
Revised 5 December 2011
Accepted 9 December 2011
Available online 17 December 2011

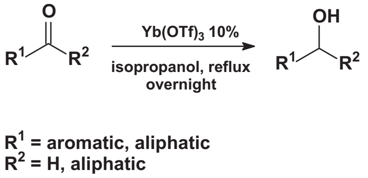
Keywords:
Carbonyl compounds
Heterogeneous catalysis
Meerwein–Ponndorf–Verley reaction
Reduction
Ytterbium triflate

ABSTRACT

Ytterbium triflate was shown to be effective in promoting the reduction of substituted aromatic and aliphatic aldehydes and ketones using isopropanol as the solvent and the reducing agent. The whole process furnished the desired adducts in 22-98% yield.

The reduction of carbonyl compounds into the corresponding alcohols is well recognized as one of the most effective and valuable chemical processes both in industry and in the chemical laboratory environment. Aldehydes and ketones can be converted to primary and secondary alcohols, respectively, using different reducing agents like metal alkoxides in isopropanol or other alcohols, metal hydrides, catalytic hydrogenation, alkaline metals and ethanol and several others. The metal alkoxide-based methodology is the well known Meerwein–Ponndorf–Verley (MPV) reaction that is among the oldest synthetic method described for the first time in 1925.[1,2] The MPV process involves the transfer of a hydrogen atom to a carbonyl group. As stated before metal alkoxides are often used as promoters of this reaction.[3] The disadvantages of the original experimental protocol and of its closest versions mainly concern the use of a large excess of metal alkoxides to efficiently promote the reaction and to get appreciable yields of adducts, that in turn leads to difficulties for their removal and separation. This also does not render the overall process an environmentally friendly one. Several other homogeneous and heterogeneous catalysts for the MPV reaction have been developed. These include dimethyl- and trimethylaluminium chloride,[4] complexes of iridium,[5] ruthenium,[6] plutonium[7] and samarium,[8] bimetallic alkoxides,[9] Al-free Zr zeolites,[10] supported Zr propoxide,[11] MCM-41-grafted Al isopropoxide,[12] Al_2O_3,[13] ZrO_2,[14] MgO,[15,16] Mg–Al[17] and Ca–Al[18] mixed oxides and finally Yb isopropanolate.[19] In recent years some experimental protocols to perform the title reaction either in acidic[20] or basic medium[21] in the absence of any catalyst have been reported, although some doubts about the effectiveness of these uncatalysed processes have arisen.[22] Moreover the MPV reaction has been successfully employed in the synthesis of biologically natural products.[23] Finally the reported methodologies for the MPV reaction have been recently exhaustively reviewed.[24–27] The large number of reports about the title chemical process witness for a field of research in the context of organic synthesis of current and growing interests.

During the last two decades, rare earth metal triflates have been found to be unique Lewis acids since they are water tolerant recyclable catalysts and can effectively promote several carbon–carbon and carbon–heteroatom bonds formation reactions in high yields often in the frame of a green chemical approach.[28] In continuation of our ongoing studies aimed at developing mild and practical protocols for the synthesis of useful building blocks and/or biologically active compounds by using lanthanides as catalysts, herein we



Scheme 1. Yb(OTf)$_3$ catalysed MPV reduction of carbonyl compounds.

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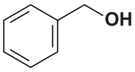
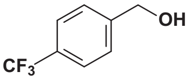
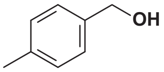
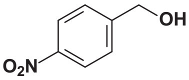
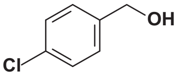
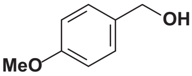
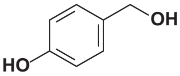
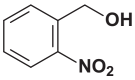
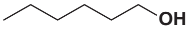
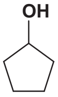
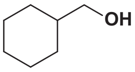
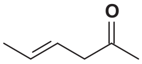
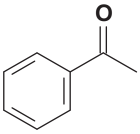
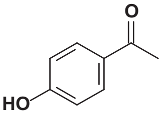
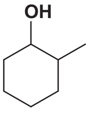
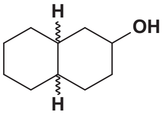
doi:10.1016/j.tetlet.2011.12.033

wish to report that the MVP reaction can be effectively catalysed by $Yb(OTf)_3$ hydrate in discrete to very good yields using differently substituted aromatic and aliphatic aldehydes and ketones and isopropanol as the solvent and the reducing agent (Scheme 1).

In a preliminary experiment, benzaldehyde (1.0 mmol) and ytterbium triflate hydrate (0.1 mmol) were dissolved in *i*PrOH (2 mL). The resulting mixture was vigorously stirred at reflux overnight. After evaporation of the solvent by anhydrous N_2 bubbling into the reaction medium, crystallization and recovery of the catalyst by filtration, and finally purification by flash chromatography, benzyl alcohol was obtained in a 98% yield. Encouraged by the results recorded using benzaldehyde as the substrate, we applied the same reaction conditions to other differently substituted aromatic and aliphatic aldehydes and ketones. The corresponding primary and secondary alcohols were obtained in discrete to good yields as reported in Table 1.

Table 1
$Yb(OTf)_3$ catalysed MPV reduction of selected carbonyl compounds[29]

Entry	R^1	R^2	Product	Yield[a] (%)
1	Ph	H		98
2	pCF_3–Ph	H		62
3	pCH_3–Ph	H		67
4	pNO_2–Ph	H		96
5	pCl–Ph	H		68
6	$pOCH_3$–Ph	H		22
7	pOH–Ph	H		Traces
8	oNO_2–Ph	H		39
9	*n*-Pentyl	H		87
10	*c*$(CH_2CH_2CH_2CH_2)$			74
11	*c*$(CH_2CH_2CH_2CH_2)CH$			63
12	$CH_3CH{=}CHCH_2$	CH_3		54
13	Ph	CH_3		51
14	pOH–Ph	CH_3		Traces
15	2-CH_3*c*$(CHCH_2CH_2CH_2CH_2)_4$			41[b]
16	*cis*/*trans* 2-Decalone			40

[a] Yields of pure isolated products, characterised by GC–MS, ^1H NMR and ^{13}C NMR.
[b] 83:17 Mixture of *trans*/*cis* isomers.

Both aromatic aldehydes having electron donating or withdrawing substituents as well as aliphatic aldehydes and ketones reacted in most cases to the same extent furnishing the desired adducts in yields ranging from 40% to 98%. The only exceptions are represented by *p*-anisaldehyde (entry 6), *p*-hydroxybenzaldehyde (entry 7), *o*-nitrobenzaldehyde (entry 8) and *p*-hydroxyacetophenone (entry 14). Trying to explain this discrepancy in reactivity, it may be hypothesized that for *p*-anisaldehyde and *p*-hydroxybenzaldehyde the coordination of the oxygen atom in the *para* position of the aromatic ring to Yb^{+3}, leading to a decrease of the catalytic efficiency of the Lewis acid, may be evoked. The tendency of trivalent Yb and lanthanide in general to be coordinated by phenols is in fact widely reported in the literature.[30] On the other hand the lower yield obtained when *o*-nitrobenzaldehyde was used as the substrate may be explained by the steric hindrance exerted by the $–NO_2$ group in the *ortho* position to the coordination of the metal centre to the oxygen atom of the aldehyde function thus diminishing its reactivity and preventing its interaction with the reducing agent. The catalyst was recovered by precipitation from every reaction and filtered. Recycled in this way, the catalyst could be reused several times without any significant loss of activity. For example, the reaction leading to product of entry 1 was repeated three additional times with the recovered Lewis acid with yields in benzyl alcohol of 93%, 95% and 92%, respectively.

From a mechanistic point of view, it could be hypothesized that Yb^{+3} coordinates both the carbonyl substrate and isopropanol, the latter serving as the hydride donor and being coordinated to the metal centre as an alkoxide. The hydride transfer from the secondary carbon of the alcohol to the carbonyl group may occur in a six-membered transition state in the same way as proposed by several authors in the past and recent literatures,[31–36] leading to the contemporary reduction of the aldehyde/ketone and the oxidation of isopropanol to acetone, and this could be regarded as the rate-determining step of the process. To this aim we performed also the reaction depicted in entry 1 in an NMR sealed tube using equimolar quantities of benzaldehyde and isopropanol and $CDCl_3$ as the solvent. Results from this experiment revealed the equimolar conversion to the same extent at fixed times of benzaldehyde into benzyl alcohol and isopropanol to acetone.

As a conclusion, in this Letter we have demonstrated that differently substituted aromatic and aliphatic aldehydes and ketones undergo reduction to primary and secondary alcohols under the catalysis of $Yb(OTf)_3$ hydrate in the presence of isopropanol used as the solvent and as the reducing agent. The simple workup procedure, mild reaction conditions and overall satisfactory yields make our methodology a valid and alternative contribution to the existing processes in the field of MPV reduction. To the best of our knowledge, the process described herein represents the first example of the MPV process catalysed by a Lewis acid in a homogeneous system under non-basic conditions. Further investigations to broaden the scope of this methodology are in progress in our laboratories.

Acknowledgments

Financial support from MIUR PRIN 2008 ‘A Green Approach to Process Intensification in Organic Synthesis’ and from the University ‘G. d’Annunzio’ of Chieti-Pescara is gratefully acknowledged.

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29. Experimental

    General remarks: All reagents were obtained from commercial sources (Aldrich Chemical Co.) and used without further purification. All solvents were of analytical grade. All extracts were dried over anhydrous Na_2SO_4. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (^1H NMR, 200 MHz; ^{13}C NMR, 50.32 MHz) $CDCl_3$ was used as the solvent and tetramethylsilane as an internal standard. Reactions were routinely monitored by TLC using Merck silica gel F_{254} plates and visualization of TLC spots with a freshly prepared 7% ethanolic solution of phosphomolibdic acid. Silica gel 40 (0.063–0.200 mm) from Merck was used for column chromatography. GC and GC–MS analyses were performed on a Hewlett-Packard gas chromatograph, model 5890 equipped with a FID detector and coupled to an electronic integrator. The chromatograph was fitted with methyl silicone column (12.5 m × 0.25 mm, 0.25 μm film thickness). Carrier gas was helium (purity >99%, 0.9 mL/min); injector and detector temperatures were 280 °C and 250 °C, respectively. The oven temperature was programmed from 50 to 270 °C at a rate of 10 °C/min. Quantitative data were obtained by electronic integration of FID area data without the use of response factor correction. GC/MS analyses were performed using a Hewlett-Packard 6890 chromatograph combined with HP Chemstation software, equipped with a 5973 Mass Selective Detector and mass spectrometer was operated at 70 eV, scanning speed 1 s over 40–300 amu range and an ion source temperature of 180 °C. Compounds were identified by comparison of mass spectra from the Nist98 Mass Spectral Database. GC analyses using a polar column were carried out on a Varian 3400 GC system equipped with a fused silica CP-Sil 88 column (50 mm × 0.22 mm, 0.2 μm film thickness). Carrier gas was helium (purity >99%, 0.9 mL/min). Oven temperature was programmed from 50 to 270 °C at a rate of 10 °C/min.

    General procedure: The carbonyl compound (1.0 mmol) and ytterbium triflate hydrate (0.1 mmol) were dissolved in *i*Pr-OH (2 mL). The resulting mixture was stirred at reflux overnight. The solvent was removed by anhydrous N_2 bubbling into the reaction medium, then the residue was dissolved in 10 mL of cold $CHCl_3$ and let to stand for 5 h at 4 °C. The resulting solid was removed by paper filtration and the resulting solution dried by anhydrous N_2 bubbling. The resulting crude mixture was purified by flash chromatography (elution CH_2Cl_2) affording the desired adduct.

    Analytical data of all adducts obtained by this procedure were in full agreement with those recorded for pure commercial products used for comparison.
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