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Hydrogenation of the Carbonyl Group in α-Ketoesters and α-Ketoamides Catalyzed by Ruthenium Clay

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Ruthenium clay, prepared by reaction of $RuCl_3 \cdot H_2O$ with the 3-phosphinopropyl ligand anchored on Fluka K10 montmorillonite, is an effective catalyst for the reduction of the α-carbonyl group of α-ketoesters and α-ketoamides (50−89% yield).

Introduction

Early work on the homogeneous catalytic hydrogenation of carbonyl compounds involved mainly rhodium−phosphine complexes.[1] Cationic rhodium complexes $[RhH_2L_2S_2]^+ClO_4^-$ or $[RhH_2L_2S_2]^+PF_6^-$ (S = solvent, L = phosphine ligand) were found to be effective for the reduction of simple ketones.[2] The first homogeneous asymmetric catalytic hydrogenation of ketones was performed in the presence of a rhodium complex with (*R*)-(+)-benzylmethylphenylphosphine as a ligand. Rhodium phosphine systems with a neutral phosphine ligand (BPPM, CyDIOP) were found to be effective for the reduction of α-ketocarboxylic esters,[3] α-ketoamides,[4] and ketopantolactone.[5]

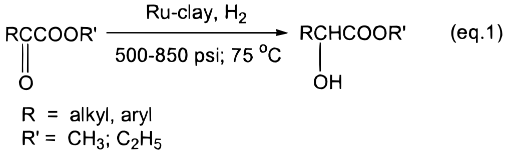
Ruthenium complexes have been used for the hydrogenation of olefins, and recently ruthenium-based complexes were found to be highly selective for the hydrogenation of carbonyl compounds (aromatic ketones, *β*-ketoesters, α-diketones, α-aminoketones, α,*β*-acetylenic ketones) in homogeneous catalysis.[6] For heterogeneous hydrogenation, which is still a very convenient synthetic method both on a micro and macro scale, the most popular catalysts are based on platinum, palladium, and nickel.[1]

The reduction of α-ketoesters and α-ketoamides has attracted considerable attention in recent years.[7] The catalytic hydrogenation of α-ketoacids and α-ketoamides were carried out using Pt/Al_2O_3, PtO_2, Pd/C, $Pd/CaCO_3$, $Pd/BaSO_4$, or Raney nickel.[1,7] A platinum-supported catalyst can be chirally modified with cinchona alkaloids or other simple nitrogen-containing compounds, and this allows the synthesis of the α-hydroxyesters and α-hydroxyamides with enantiomeric excess values of up to 84% and 60%, respectively.[7]

Results and Discussion

Previous studies in our laboratory showed that the heterogeneous system consisting of ruthenium anchored on several clays is a useful catalyst for the selective reduction of the carbon−carbon double bond of unsaturated esters, sulfones, and vinyl oxiranes.[8] We now wish to report that ruthenium clay is an effective catalyst for the reduction of the carbonyl group of α-ketoesters and α-ketoamides.

Ruthenium clay was prepared by a three-step process: reaction of Fluka K10 montmorillonite with (3-chloropropyl)trimethoxysilane, followed by treatment with $KPPh_2$, and then by reaction with $RuCl_3 \cdot H_2O$.[8] The ruthenium content varies from 0.13 to 0.17 mmol Ru/g clay for different batches of catalyst (determined by atomic absorption or ICP analysis). The reaction of α-ketoesters with hydrogen in the presence of Ru clay proceeded at 500 or 600 psi H_2 and 75 °C, affording the corresponding hydroxyesters in 60−100% conversion and 80−89% isolated yields (eq 1). For methyl pyruvate, an increase in hydrogen pressure from 500 to 600 psi results in complete conversion of the starting material to the hydroxyester (Table 1, entries 1, 2). The keto group connected to a longer alkyl chain, like in ethyl 3-methyl-2-oxobutyrate, can be reduced completely at 500 psi H_2 (Table 1, entry 3). The reduction of substrates containing



$$\underset{\substack{\|\\ O}}{RCCOOR'} \xrightarrow[\text{500-850 psi; 75 °C}]{\text{Ru-clay, } H_2} \underset{\substack{|\\ OH}}{RCHCOOR'} \qquad \text{(eq.1)}$$

R = alkyl, aryl
R' = CH_3; C_2H_5

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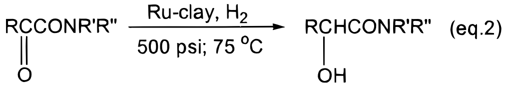
Table 1. Reduction of the Keto Group in α-Ketoesters and α-Ketoamides Using Ruthenium Clay

no.	substrate[a]	pressure (psi H_2)	time (h)	conversion (yield[b]) (%)
1.	$CH_3COCOOCH_3$	500	45	60
2.	$CH_3COCOOCH_3$	600	45	100
3.	$CH_3CH(CH_3)COCOOC_2H_5$	500	45	100 (80)
4.	$PhCOCOOCH_3$	500	24	66
5.	$PhCOCOOCH_3$	600	20	100
6.	$PhCH_2CH_2COCOOC_2H_5$	500	18	100 (87)
7.	$H_2CC(CH_3)_2C(O)C(O)O$	850	66	100 (89)
8.	$PhCON(C_2H_5)_2$	500	60	92 (50)
9.	$PhCOCONH(CH_2)_3CH_3$	500	43	100 (68)
10.	$PhCOCONHCH_2Ph$	500	50	90 (71)

[a] Reaction conditions: 1 mmol of substrate; 30 mg of Ru clay (0.005 mmol Ru); 8 mL of dry benzene; 75 °C. [b] Isolated yield. Products were identified by comparison of spectral results with literature data.[10,11]

a phenyl ring, methyl benzoylformate, and ethyl 2-oxo-4-phenylbutyrate proceeds more rapidly (24 and 18 h, respectively, Table 1, entries 4, 5, 6), resulting in complete conversion to the α-hydroxyester. A longer time and higher pressure are necessary for the reduction of ketopantolactone to pantolactone (Table 1, entry 7). Pantolactone was obtained in high yield (89%) as the sole product of the reaction. Attempts to favor the formation of one enantiomer over the other one in the case of ketopantolactone, by adding a chiral ligand ((*R*)-(+)-BINAP) to the initial reaction mixture, gave incomplete hydrogenation, without any measurable enantiomeric excess.

The results obtained for α-ketoesters prompted us to investigate the activity of the Ru catalyst for other derivatives of ketoacids such as α-ketoamides. The substrates were synthesized by the reaction of α-ketoesters with dimethylaluminum amides generated in situ from trimethylaluminum and the corresponding amine.[9] All the α-ketoamides were hydrogenated to α-hydroxyamides in high conversions (90−100%), without any competitive reactions taking place (eq 2 and Table 1, entries 8−10).



$$\underset{\overset{\|}{O}}{RCCONR'R''} \xrightarrow[500\ psi;\ 75\ ^oC]{Ru\text{-}clay,\ H_2} \underset{\overset{|}{OH}}{RCHCONR'R''} \quad (eq.2)$$

R = Ph;
R' = R'' = C_2H_5
R' = $(CH_2)_3CH_3$; R'' = H.
R' = CH_2Ph; R'' = H.

N-Butyl-benzoylformamide is reduced somewhat faster (43 h) than *N*-benzyl-benzoylformamide (50 h) and *N*,*N*-diethylbenzoylformamide (60 h). The rate of hydrogenation is probably dependent on the type of the amide, primary or secondary, and on the substituent at nitrogen, aliphatic or aromatic. But neither of the two factors have a dramatic effect on the reaction time.

In conclusion, ruthenium−phosphine−clay is an excellent catalytic system for the reduction of the α-carbonyl group in α-ketoesters and α-ketoamides. The ruthenium-based heterogeneous catalyst is stable and retains high efficiency during consecutive catalytic cycles (e.g., reuse of ruthenium clay three times involves separation of the catalyst, followed by washings with solvent, drying, and use in another reaction and resulted in 0.003 mmol Ru/100 mg clay loss but no decrease in the yield of hydrogenated product).

Experimental Section

General Considerations. All ^1H and ^{13}C NMR spectra were recorded on Varian 200 MHz Gemini and Varian XL 300 spectrometers using $CDCl_3$ as the solvent. Infrared spectra were run on a Bomem MB-100 FT-IR spectrometer. Mass spectra were obtained on a VG7070 E mass spectrometer. Solvents were dried and purified by standard methods. Column chromatography was performed with Merck Silica gel 60 using solvent combinations determined via initial TLC analysis.

The α-ketoesters were purchased from Aldrich and used as received. All the α-ketoamides were prepared from the reaction of equimolecular amounts of trimethylaluminum, amine, and α-ketoester using a procedure described previously.[9] In a typical experiment 1.2 mL (3 mmol) of 2.5 M solution of trimethylaluminum in hexane was added, at room temperature, to a solution of 3.0 mmol amine in 7 mL of dry methylene chloride, under nitrogen. The mixture was stirred for 20 min at room temperature, and then 3.0 mmol of α-ketoester was added. The flask containing the mixture was kept at 30 °C, and the progress of the reaction was followed by TLC. The reaction times varied, according to the substrates used, from 5 to 23 h. The reaction was quenched with dilute HCl and extracted with methylene chloride. The organic phase was dried ($MgSO_4$) and concentrated by rotary evaporation. The α-ketoamide was obtained from the reaction mixture by silica gel column chromatography using different ratios of hexane/ethyl acetate as eluant. The products were characterized by NMR (^1H,^{13}C), IR, and MS methods and compared with literature data.[9]

General Procedure for the Hydrogenation Reactions. A mixture of the substrate (1 mmol) and ruthenium clay (30 mg, 0.005 mmol Ru) in dry benzene (8 mL) was placed in a 45 mL autoclave equipped with a glass liner and a magnetic stirrer. The autoclave was purged three times with hydrogen and then pressurized at the desired level. The reactor was placed in an oil bath and maintained at constant temperature. To stop the reaction the autoclave was cooled to room temperature, and the excess hydrogen gas was released. The reaction mixture was filtered through Celite to retain the ruthenium clay, and then the solvent was removed by rotary evaporation of the filtrate. In the case of recycling the catalyst, the mixture was filtered through fine filter paper, and the ruthenium clay was then washed several times with benzene, followed by THF, and subsequently vacuum-dried. The purification of the products was made by silica gel column chromatography using different ratios of the mixture hexane−ethyl acetate as eluant. The compounds obtained were characterized by ^1H and ^{13}C NMR, FT-IR, and MS, and the results were in accord with the data for commercial products (when available) or literature data.[10,11]

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