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RHODIUM CATALYZED REDUCTIVE ESTERIFICATION REACTIONS

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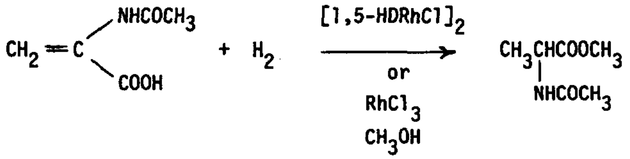
Summary: Reductive esterification occurs when unsaturated acids are treated with hydrogen in alcohol using either rhodium trichloride or the dimer of chloro(1,5-hexadiene)rhodium(I) as the catalyst. Saturated acids containing appropriate functional groups are also esterified under the same conditions.

Rhodium complexes are one of the most useful classes of catalysts for the homogeneous hydrogenation of unsaturated substrates.[2] Numerous publications have appeared, including ones concerned with the selective reduction of the double bond of olefins containing other functional groups located near the unsaturated moiety. For instance, treatment of α,β-unsaturated acids (e.g. p-methylcinnamic acid) with hydrogen and a catalytic amount of chlorotris(triphenylphosphine)rhodium(I) in benzene at 60° and 60-80 psi affords the corresponding saturated acids[3]. We now wish to report that a variety of unsaturated acids experience reductive esterification when subjected to hydrogenation in alcohol using a rhodium(I) or rhodium(III) catalyst, and that certain unsaturated acids can also undergo esterification under the same conditions.

When 2-acetamidoacrylic acid (1) was treated with hydrogen and a catalytic quantity of chloro(1,5-hexadiene)rhodium(I) dimer in methanol, overnight at room temperature and one atmosphere, the saturated ester 2 was formed in 96% yield. The ratio of substrate to catalyst used was 25:1. Rhodium trichloride was equally effective as a catalyst for this reductive



(1) (2)

esterification reaction, while rhodium black catalyzed reduction but not esterification affording N-acetylalanine. No reaction occurred in the absence of hydrogen (see results for 1 and for N-acetylalanine in Table 1), suggesting that a rhodium hydride is the key catalytic species for both reduction and esterification.

Simple α,β-unsaturated acids (not having an amide function) such as trans-2-octenoic acid also undergo reductive esterification in fine yield (see Table 1 for data). In order to achieve esterification of the acid function, a unit capable of complexing to rhodium in a π- or σ-fashion must be present at an appropriate location in the substrate. This requirement is clearly demonstrated by the formation of methyl n-butyrate in quantitative yield from 3-butenoic acid, while n-butyric acid was inert under the same reaction conditions. In addition, hydrogenation of oleic acid in methanol, using $RhCl_3$ as the catalyst, gave the saturated acid (n-heptadecanoic acid). Amido acids were esterified in good yields including N-acetylalanine, N-acetylmethionine, and N-acetylglutamic acid with both acid functions undergoing reaction in the latter case.

When an aryl group is present in the reactant, then reduction of the arene ring occurs under the reaction conditions, together with hydrogenation of the double bond (if present) and esterification [α-acetamidocinnamic acid, p-methylcinnamic acid, N-acetyl-L-phenylalanine, α-methoxyphenylacetic acid). These rhodium catalysts have been used previously for the hydrogenation of aromatic hydrocarbons under phase transfer catalysis conditions[4,5].

Let us consider the pathway outlined in Scheme 1 as a working hypothesis for the esterification of N-acetylalanine using $[1,5\text{-HDRhCl}]_2$ as the catalyst. Oxidative addition of hydrogen to the catalyst can afford the rhodium (III) complex 3 [L can be a double bond of the diene, or a solvent molecule]. A rhodium hydride would be generated in the reaction of rhodium chloride and hydrogen.[6] Complex 3 may react with N-acetylalanine to form the chelating rhodium carboxylate 4, with loss of hydrogen. Precedence for a carboxylic acid-rhodium hydride reaction comes from the work of Robinson and Uttley[7], who showed that acetic acid reacts with $HRh(PPh_3)_4$ or $HRh(CO)(PPh_3)_2$ in ethanol to give the monodentate metal carboxylate. Reaction of 4 with methanol would generate the ester and the rhodium hydroxide complex 5. The hydride 3 could then be regenerated by exposure of 5 to hydrogen.

The following general procedure was used: A mixture of the substrate [3.20 mmol] and rhodium trichloride trihydrate [0.029 g, 0.128 mmol - or $[1,5\ \text{HDRhCl}]_2$] in methanol [10 ml.] was stirred under hydrogen for 24 hours. The reaction mixture was filtered, the solvent was removed by rotary evaporation, and pure ester was isolated by treatment with ether, washing with water, drying the ether layer ($MgSO_4$), followed by removal of the ether and then distillation or silica gel thin-layer chromatography.

TABLE 1

Rhodium Catalyzed Reductive Esterification Reactions[a]

Substrate	Catalyst[b]	Alcohol	Product, %[c]
(1)	A	CH_3OH	(2), 96
	B	CH_3OH	(2), 96 (91)[e]
	B[d]	CH_3OH	-
	A	C_2H_5OH	$CH_3\overset{NHCOCH_3}{C}HCOOC_2H_5$, 50
	C	CH_3OH	$CH_3\overset{NHCOCH_3}{C}HCOOH$, 100
$PhCH{=}\overset{NHCOCH_3}{C}{-}COOH$	B	CH_3OH	$C_6H_{11}CH_2\overset{NHCOCH_3}{C}HCOOCH_3$, 75
trans-p-$CH_3C_6H_4CH{=}CHCOOH$	B	CH_3OH	4-$CH_3C_6H_{10}CH_2CH_2COOCH_3$, 94
trans-$CH_3(CH_2)_4CH{=}CHCOOH$	B	CH_3OH	$CH_3(CH_2)_6COOCH_3$, 90(82)[e]
$CH_3(CH_2)_7CH{=}CH(CH_2)_6COOH$	B	CH_3OH	$CH_3(CH_2)_{15}COOH$, 98
$CH_2{=}CHCH_2COOH$	B	CH_3OH	$C_3H_7COOCH_3$, 100
	B	C_2H_5OH	$C_3H_7COOC_2H_5$, 91
C_3H_7COOH	B	CH_3OH	-
$CH_3\overset{NHCOCH_3}{C}HCOOH$	A	CH_3OH	$CH_3\overset{NHCOCH_3}{C}HCOOCH_3$, 95
	A[d]	CH_3OH	-
	B	CH_3OH	$CH_3\overset{NHCOCH_3}{C}HCOOCH_3$, 92
$HOOCCH_2CH_2\overset{NHCOCH_3}{C}HCOOH$	B	CH_3OH	$CH_3OOCCH_2CH_2\overset{NHCOCH_3}{C}HCOOCH_3$, 100
$CH_3SCH_2CH_2\overset{NHCOCH_3}{C}HCOOH$	B	CH_3OH	$CH_3SCH_2CH_2\overset{NHCOCH_3}{C}HCOOCH_3$, 58
$PhCH_2\overset{NHCOCH_3}{C}HCOOH$	B	CH_3OH	$C_6H_{11}CH_2\overset{NHCOCH_3}{C}HCOOCH_3$, 75
$Ph\overset{OCH_3}{C}HCOOH$	A	CH_3OH	$C_6H_{11}\overset{OCH_3}{C}HCOOCH_3$, 82[f]
	B	CH_3OH	$C_6H_{11}\overset{OCH_3}{C}HCOOCH_3$, 95[g]

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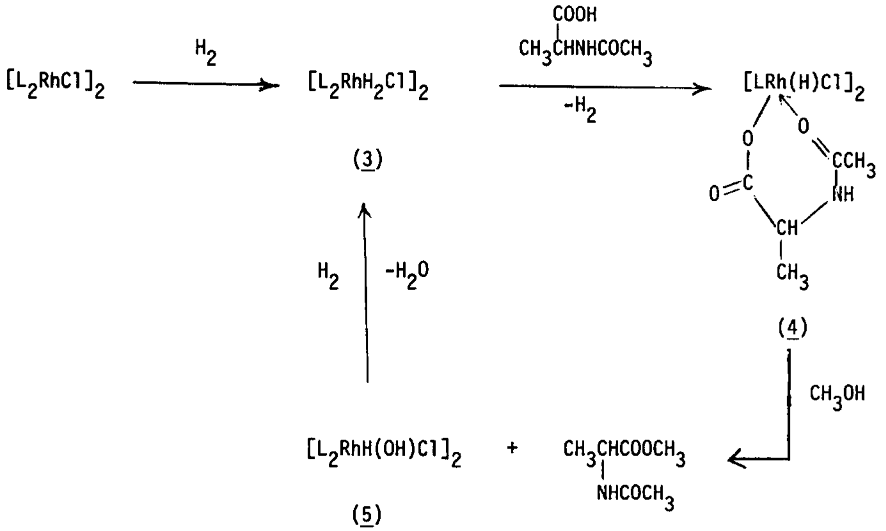
[a] Products were identified by comparison of spectral data [ir, nmr (^1H, ^{13}C), ms] with those for authentic materials and/or with literature data. [b] A=$[1,5HDRhCl]_2$; B=$RhCl_3$; C=Rh black [c] Yields determined by gas chromatography with internal standard. [d] No H_2. [e] Isolated yield. [f] $C_6H_{11}CH_2COOCH_3$, 16%. [g] $C_6H_{11}CH_2COOCH_3$, 5%.

In conclusion, rhodium chloride and the dimer of chloro(1,5-hexadiene)rhodium are fine catalysts for reductive esterification reactions. Therefore, this reaction is useful when one needs to reductively esterify an α,β or β,γ-unsaturated acid. Furthermore, it is a novel method for the esterification of saturated acids containing suitable functionalities [amide, ether, thioether] which are required to promote esterification (via coordination) but which are unchanged at the end of the reaction. The reactions described above occur under very mild conditions, and are simple both in terms of execution and work-up.

Scheme 1



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