Ruthenium Complex catalysed Condensation of Nitriles with Alcohols

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The $[RuH_2(PPh_3)_4]$ catalysed condensation of nitriles with alcohols in the presence of 1–2 equiv. of water proceeds under neutral conditions to give the corresponding esters and lactones highly efficiently along with evolution of ammonia.

Although transformations of the cyano functionality of nitriles in acidic or basic media afford a variety of important compounds,[1] neutral and mild conditions still need to be developed. During our studies on the activation of the C≡N unit of nitriles with metal complex catalysts, we found that low-valent ruthenium hydride complexes are excellent catalysts which show unusual and specific Lewis acidity towards nitriles under neutral conditions.[2] We now report a novel catalytic condensation of nitriles with alcohols under neutral conditions. Thus, the ruthenium catalysed reaction of nitriles with alcohols in the presence of 1–2 equiv. of water gives the corresponding esters along with evolution of ammonia [eqn. (1)]. Although several methods for conversion of nitriles to esters with metal catalysts have been reported,[3] the reactions generally require severe conditions and proceed with low selectivity of the product esters without evolution of ammonia. The present reaction has advantages over the previous methods in its high efficiency, neutral conditions, cleanness with generation of ammonia and facile isolation of the desired products without any washing process.

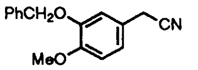
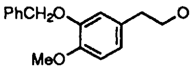
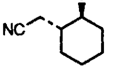
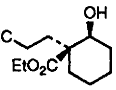
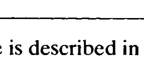
$$R^1CN + R^2OH + H_2O \xrightarrow{RuH_2(PPh_3)_4\,(cat.)} R^1CO_2R^2 + NH_3 \qquad (1)$$

The catalytic activity of various metal complexes has been examined. Dodecanenitrile was treated with methanol (4 equiv.) and H_2O (1 equiv.) in the presence of a catalyst (3 mol%) in 1,2-dimethoxyethane at 180 °C for 24 h in a sealed tube under argon. $[RuH_2(PPh_3)_4]$ was the most effective catalyst (conversion 100%; yield of methyl dodecanoate 100%). $[RuH_2(CO)(PPh_3)_3]$ also shows catalytic activity (85%; 71%); however, the use of other catalysts such as $[RhCl(PPh_3)_3]$ (29%; 0%), $[PdCl_2(PPh_3)_2]$ (24%; 4%), $CuCl_2$ (24%; 2%), and $[Mo(CO)_6]$ (18%; 0%) gave unsatisfactory results. 1,2-Dimethoxyethane proved to be a good solvent although non-polar solvents such as toluene, hexane and chloroform retarded the reaction.

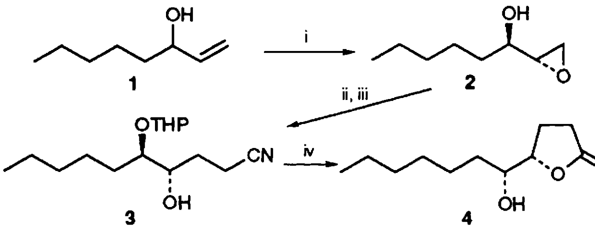
Representative results for ester formation from nitriles and alcohols are summarized in Table 1. The reaction is a useful method for the single-step preparation of esters from nitriles under neutral conditions. Acetylation of alcohols with acetonitrile can be performed conveniently without any washing process (entry 1). A variety of perfume esters (entry 1: peach- and rose-like; entry 2: apple-, banana-, and pineapple-like; entry 4: rose- and musk-like fragrance)[4] can be readily prepared from nitriles and alcohols. The intramolecular version of the present reaction provides an efficient method for synthesis of lactones. The reaction of 4- and 5-hydroxynitriles can proceed smoothly at 140 °C to give five- and six-membered lactones in excellent yields. α,ω-Hydroxynitriles except 4- and 5-hydroxynitriles undergo intermolecular condensation to give the corresponding polyesters.[5] In a typical example, a mixture of hexanenitrile (0.145 g, 2.0 mmol), 2-methylpropanol (0.191 g, 2.0 mmol), H_2O (0.037 g, 2.1 mmol), and $[RuH_2(PPh_3)_4]$ (0.067 g, 0.06 mmol) in 1,2-dimethoxyethane (0.5 ml) was heated at 180 °C for 24 h in a sealed tube under argon. Removal of the solvent followed by kugelrohr distillation (bp 60–70 °C at 1 mmHg) gave 2-methylpropyl hexanoate (0.244 g, 72%) as a colourless liquid.

The efficiency of the reaction is illustrated by the short-step synthesis (Scheme 1) of (4*S*,5*R*)-4,5-dihydroxydecanoic acid γ-lactone **4**, which is the autoregulator of anthracycline biosynthesis isolated from strains of *Streptomyces griceus*.[6,7] Sharpless epoxidation[8] of oct-1-en-3-ol **1** with (−)-dicyclohexyl tartrate (DCHT) gave epoxy alcohol **2** {conv. of **1**, 40%, isolated yield 35%, $[\alpha]_D^{28}$ −18.9 (*c* 7.5, CH_2Cl_2), 95% enantiomeric excess (e.e.)}. Tetrahydropyranyl (THP) protection of the hydroxy group followed by alkylation upon treatment with acetonitrile and lithium diisopropylamide (LDA) afforded hydroxy nitrile **3** in 55% yield {$[\alpha]_D^{23}$ +1.7 (*c* 6.2, CH_2Cl_2)}. Treatment of **3** with 2 equiv. of water in the presence of $[RuH_2(PPh_3)_4]$ catalyst at 140 °C gave **4** in 91% yield {$[\alpha]_D^{25}$ +9.8 (*c* 1.4, CCl_4), lit.,[7] $[\alpha]_D$ +11 (*c* 1.37, CCl_4)}. The e.e. was 95% as determined by 500 MHz ^1H NMR analysis of the ester of (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.

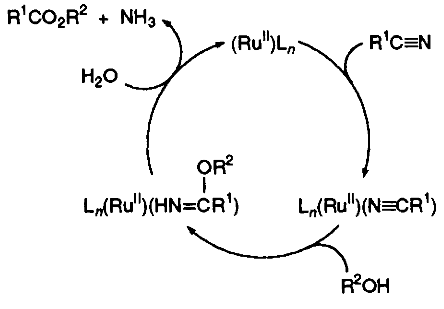
Table 1 Ruthenium catalysed reaction of nitriles with alcohols[a]

Entry	Nitrile	Alcohol	Yield of ester[b,c] (%)
1	MeCN[d]	$PhCH_2CH_2OH$	73
2	$C_5H_{11}CN$	Me_2CHCH_2OH	72
3	$C_{11}H_{23}CN$	MeOH[e]	86
4	$PhCH_2CN$	Me_2CHCH_2OH	57
5			48
6			89[f]
7			91[f]
8			73[f]

[a] The procedure is described in the text. [b] Isolated yield based on the starting nitrile. [c] All products gave satisfactory IR, NMR and mass spectral data and elemental analyses. [d] 1.5 Equiv. [e] 4.0 Equiv. [f] Reaction temperature: 140 °C; 2 equiv. of H_2O was used.



Scheme 1 *Reagents and conditions*: i, $Ti(OPr^i)_4$, Bu^tOOH, (−)-DCHT, −20 °C; ii, dihydropyran, pyridinium toluene-*p*-sulfonate 20 °C; iii, LDA, MeCN, −78 °C; iv, $[RuH_2(PPh_3)_4]$, H_2O, 140 °C



Scheme 2 Proposed mechanism of the ruthenium catalysed reaction of nitriles with alcohols

The present reaction can be rationalized by assuming the catalytic cycle shown in Scheme 2. Coordination of the nitrile to the Ru^{II} complex followed by nucleophilic attack of the alcohols gives the imidate ruthenium complex,[9] which undergoes hydrolysis to give the ester, ammonia and Ru^{II} complex to complete the catalytic cycle.

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