Rhodium-Catalyzed Michael Additions of Activated Nitriles to α,β - Unsaturated Esters

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Key Words: Michael additions; conjugated additions of activated nitriles; conjugated additions catalyzed by transition-metal complexes; homogeneous catalysis; rhodium complexes as catalysts.

Abstract: The Michael additions of activated nitriles to methyl acrylate (MA) and methyl vinyl ketone (MVK) proceeds with fair-to-high yields (46-92%) in the presence of catalytic amount of HRh(CO)(PPh3)3 1 under mild eaction conditions.

The transition-metal complex-catalyzed Michael addition has raised growing interest during the last years ¹⁻⁶. Copper, palladium, nickel and cobalt derivatives have proved to display a good catalytic activity towards this important type of carbon-carbon bond forming reaction. Homochiral compounds such as diamines, aminoalcohols, Schiff-bases are used as ligands to form, with the afore mentioned metals, catalytic complexes, which produce, using appropriate reaction partners, optically active Michael adducts with up to 70% enantiomeric excess⁷⁻¹¹. Recently, it has been reported that ruthenium-phosphine complexes, such as H₂Ru(PPh₃)4, are also effective catalysts for the addition of activated nitriles to α , β -unsaturated carbonyl compounds ¹². Now, we have found that an analogous addition reaction can be conveniently performed under neutral and mild conditions in the presence of a catalytic amount of HRh(CO)(PPh₃)₃, the popular Wilkinson's hydroformylation catalyst:

Scheme 1

$$R-CH_2-CN + CH_2=CH-COX \xrightarrow{[Rh]} R-CH-CH_2-CH_2-CH_2-COX CN$$

 $R = C_6H_5$ -, C_2H_5OCO - or -C=N

 $X = CH_3O$ - or -CH₃

The Michael reactions were carried out at temperature not exceeding 50°C under nitrogen atmosphere, using a nitrile-to-rhodium complex molar ratio 100:1 and an excess of the Michael acceptor, according to the following experimental general procedure: the catalytic complex 1 (0.022 mol) was dissolved in 7 ml of anhydrous toluene; then malononitrile (2.2 mmol) and MVK (4.4 mmol) were added. The homogeneous reaction mixture was stirred at room temperature for seven hours and then the solvent was evaporated *in vacuo*. The Michael adduct was isolated and purified by flash chromatography using the mixture n-hexane/diethyl ether = 9/1 as the eluant. The chemical yield, determined on the isolated product, was 92%.

All the Michael adducts were identified by their NMR and mass spectroscopy spectral data.

The presence of the solvent reduces considerably the reaction rates but it is necessary when the Michael acceptor MVK is used because of the high reaction rate even at 0°C.

Representative results are shown in Table 1.

Table 1. Michael Additions of Nitriles to α,β-Unsaturated Esters or Ketones Catalyzed by HRh(CO)(PPh3)3

Exp.	Michael donor	Michael acceptor	Temp. (°C)	Time (h)	Yield ^a (%)
1	Ph-CH ₂ -CN	CH2=CH-COOMe	20	6	41b
2	**	**	50	6	46 ^c
3	**	CH3-CH=CH-COOEt	50	24	0
4d	**	CH2=CH-CO-CH3	0	7	68
5d	**	**	20	3	85
6d	**	CH2=CH-CN	20	24	0
7d	**	Ph-CH=CH-CO-CH3	20	24	0
8	EtO2C-CH2-CN	CH2=CH-COOMe	20	6	91
9	11	CH3-CH=CH-COOEt	50	24	0
10		Ph-CH=CH-COOMe	50	48	7
11	"	Ph-CH=CH-COOEt	50	24	21
12	CH ₃ CN	CH2=CH-COOMe	50	24	0
13d	••	CH2=CH-CO-CH3	20	24	0
14d	**	"	50	24	0
15d	NC-CH2-CN	CH2=CH-COOMe	20	2	89
16 ^d	*1	CH2=CH-CO-CH3	0	7	92

Michael donor: 2.2 mmol; Michael acceptor: 4.4 mmol; HRh(CO)(PPH3)3: 0.022 mmol.

^a: Isolated product yield based on the starting nitrile.

b: 12.5% of unidentified high boiling by-products are also present.

c: 25.6% of unidentified high boiling by-products are also present.

d: Experiments carried out in the presence of toluene (7 ml).

The highest yields were achieved using strongly activated nitriles, like ethyl cyanoacetate or malononitrile, as Michael donors (Exp. 8, 15 and 16); acetonitrile did not react under the same reaction conditions using both MA or MVK as Michael acceptor (Exp. 12, 13 and 14). However benzyl cyanide showed a very good activity with MVK even at 0°C (Exp. 4). The same cyanide is quite unreactive towards conjugate addition to acrylonitr. (Exp. 6), probably due to the well-known ability of acrylonitrile to form stable complexes with rhodium ^{13,14}.

The chemoselectivity of the reaction is generally very high (> 98%) except in the case of the Michael addition of benzyl cyanide to MA because of the formation of high boilig by-products, very likely arising from rhodium-catalyzed MA dimerization 15 .

In any case the Michael adducts do not undergo neither retro-Michael reaction nor undesired transformations under the reaction conditions used.

All the reactions were also performed in the absence of HRh(CO)(PPh3)3 but no Michael adduct was detected.

As in the case of alkene hydrogenation ¹⁶, the catalytic complex is extremely sensitive to the steric hindrance exerted by the Michael acceptor: other α , β -unsaturated esters, like ethyl crotonate or methyl cinnamate, or α , β -unsaturated ketones, like benzalacetone, gave quite unsatisfactory results (Exp. 3, 9 and 7).

Attempts of performing asymmetric Michael additions of benzyl cyanide to MVK catalyzed by the *in situ* complex 1/PPM [PPM = (2S,4S)-(-)-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine] gave chemical yields around 60%, but no optical induction. This result indicates that this chiral catalytic precursor gives rise to species unable to discriminate between the enantiotopic hydrogen atoms of benzyl cyanide.

Other Rh(I)-complexes like [Rh(COD)Cl]₂ both alone and in the presence of PPh₃ or 1,4bis(diphenylphosphino)butane (ligand-to-metal molar ratio 2:1 and 1:1, respectively) are uneffective, pointing out the important role of a preformed hydrido-species played in this type of catalytic reaction.

The present rhodium-catalyzed reaction can be rationalized by assuming the following pathway for the catalytic process:

i) conjugated addition of HRh(CO)(PPh3)3 to the unsaturated ester or ketone under simultaneous PPh3 dissociation;

ii) oxidative addition of the low-valent rhodium species into the C-H bond adjacent to the cyano group;

iii) splitting of the Michael product from the intermediate complex *via* reductive elimination and formation of the starting catalytically active hydrido-complex.

The regioselective addition of the rhodium-hydride complex to the olefinic double bond of the Michael acceptor, involving an interaction between the metal center and the most electrophile carbon atom, could be promoted by steric rather than electronic factors ¹⁷.

The occurrence of a Rh(I)-insertion into the C-H bond activated by the cyano function is supported by the fact that less activated nitriles, such as acetonitrile, are unreactive under the same conditions and that the chemical yield of the Michael product increased with increasing the α -hydrogen mobility (see Table 1).

Other mechanistic schemes, however, cannot be ruled out, including the one that invokes the formation of an intermediate complex between the metal and a deprotonated Michael donor, which subsequently reacts out of the metal coordination sphere with the Michael acceptor: this reaction pathway seems to be operative in the addition of 1,3-dioxocompounds or their analougues to activated olefinic double bonds ¹⁰, ¹⁸.

Further work is currently in progress to document the synthetic utility of the above disclosed Michael reaction and to gain information about its mechanism.

Acknowledgment. This work was financially supported by the 40% Italian MURST fund.

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(Received in UK 18 March 1991)