Journal of Organometallic Chemistry, *448* (1993) 215–218

JOM 23120

Transition metal polyhydrides-catalyzed addition of activated nitriles to aldehydes and ketones via Knoevenagel condensation

Yingrui Lin, Xianchao Zhu, Min Xiang

Laboratary of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, 200032 Shanghai (China)

(Received June 12, 1992; in revised form July 31, 1992)

Abstract

Transition metal polyhydrides and dihydrogen complexes catalyze Knoevenagel addition of cyanoacetate to aldehydes and ketones under neutral and mild conditions, the adducts undergo dehydration to give substituted (*E*)-2-cyano-α,β-unsaturated esters exclusively.

Knoevenagel condensation of carbonyl compounds with compounds containing an active methylenic group are one of the most important methods of preparing tri-substituted alkenes in organic synthesis. The reaction is generally catalyzed by bases or Lewis acids [1]. Recently, Murahashi and Paganelli *et al.* reported Ru- [2] and Rh- [3] catalyzed aldol and Michael additions of activated nitriles to carbonyl compounds of α,β-unsaturated esters under neutral conditions. The mechanism of these reactions presumably involves an oxidative addition of the C–H bond adjacent to the cyano group to metal. Such C–H bond activation has been produced in the Murahashi reaction and an active intermediate has recently been isolated and determined by X-ray structure analysis [4]. Here we wish to report an analogous oxidative addition reaction catalyzed by the use of iridium polyhydride and ruthenium dihydrogen complex under neutral condition (eqn. (1)). This is a new example of the application of polyhydrides and dihydrogen complexes in the aldol type reaction in addition to dehydrogenation [5], transfer hydrogenation [6], and isomerization [7].

$$\underset{(2)}{R_1CH_2CN} + \underset{(3)}{R_2COR_3} \xrightarrow[\text{THF}]{MH_nL_m\ (1)} R_2R_3C{=}CR_1CN + H_2O \qquad (1)$$

$$\begin{aligned}&(4)\ R_1{=}COOEt\\&(5)\ R_1{=}CN\end{aligned}$$

1. Results and discussion

When ethyl cyanoacetate (**2**) and aldehydes or ketones (**3**) were refluxed under argon with a catalytic amount of Ir-polyhydride (**1A**) in THF, the Knoevenagel condensation products were isolated with high stereoselectivity in 70–95% yield after chromatographic purification. Using the Ru–dihydrogen complex (**1B**), a similar reaction occurred at room temperature. The results are shown in Tables 1 and 2.

There is a wide range of electrophilic carbonyl compounds. The aldehydes may be aromatic, aliphatic and may contain a double bond. The reaction was not affected by the electronic properties of the substituents on the aromatic aldehyde (see entries 5–11 in Table 1). When unsaturated cinnamaldehyde was reacted with ethyl cyanoacetate, the ethyl 2-cyano-5-phenyl-(2*E*, 4*E*)-pentadienoate was stereoselectively obtained in 85% yield, the nucleophilic attack being at the carbonyl carbon. The stereochemistry of the olefination for the other aldehydes was determined to be *E*-form exclusively by means of NMR spectra and GLC analysis. In the reaction of ketones with the cyanoacetate, cyclic ketones gave more satisfactory results than acyclic ketone except in the case of the sterically hindered cyclic ketone (entry 4 in Table 2).

When active methylene compounds with an electron withdrawing group such as ethyl malonate acetylacetone were treated under analogous conditions, no adduct was obtained. We found that the active methylene compounds containing only the cyano group as a nucleophile were effective. For instance, the treatment

---

Correspondence to: Dr. Y. Lin.

0022-328X/93/$6.00

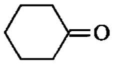
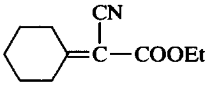
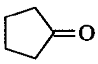
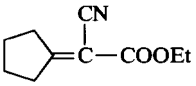
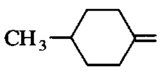
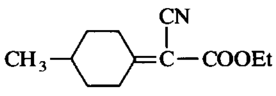
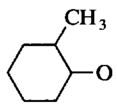
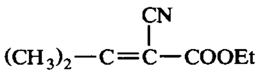
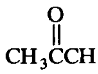
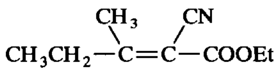
TABLE 1. Polyhydrides-catalyzed Knoevenagel reaction of **2** and aldehydes

Entry	Aldehydes		Catalyst [a]	Time (h)	Yield (%) [b]	Products [c]	
1	PhCHO	**3a**	**1A**	24	82	PhCH=C(CN)COOEt	**4a**
2	PhCHO	**3a**	**1B**	24	88	PhCH=C(CN)COOEt	**4a**
3	PhCHO	**3a**	**1C**	24	67	PhCH=C(CN)COOEt	**4a**
4	PhCHO	**3a**	**1A**	24	80	$PhCH=C(CN)_2$	**5a**
5	p-$Me-C_6H_4CHO$	**3b**	**1A**	40	85	p-$Me-C_6H_4-CH=C(CN)COOEt$	**4b**
6	p-$CH_3O-C_6H_4CHO$	**3c**	**1A**	37	87	p-$CH_3O-C_6H_4-CH=C(CN)COOEt$	**4c**
7	p-$CH_3O-C_6H_4CHO$	**3c**	**1A**	40	93	p-$CH_3O-C_6H_4-CH=C(CN)_2$	**5c**
8	p-$Cl-C_6H_4CHO$	**3d**	**1A**	48	87	p-$Cl-C_6H_4-CH=C(CN)COOEt$	**4d**
9	p-$Cl-C_6H_4CHO$	**3d**	**1B**	48	93	p-$Cl-C_6H_4-CH=C(CN)COOEt$	**4d**
10	p-$F-C_6H_4CHO$	**3e**	**1A**	48	93	p-$F-C_6H_4-CH=C(CN)COOEt$	**4e**
11	p-$O_2N-C_6H_4CHO$	**3f**	**1A**	48	84	p-$O_2N-C_6H_4-CH=C(CN)COOEt$	**4f**
12	PhCH=CHCHO	**3g**	**1A**	40	85	PhCH=CH-CH=C(CN)COOEt	**4g**
13	$(CH_3)_2CHCHO$	**3h**	**1A**	60	63	$(CH_3)_2CH-CH=C(CN)COOEt$	**4h**
14	$(CH_3)_2CHCHO$	**3h**	**1B**	48	70	$(CH_3)_2CH-CH=C(CN)COOEt$	**4h**

[a] Cat. = 1.0 mol%, **1A** = IrH_5 ($^iPr_3P)_2$, **1C** = ReH_7 ($^iPr_3P)_2$, reacted at 65°C. **1B** = $RuH_4(Ph_3P)_3$, reacted at 25°C.
[b] Isolated by column chromatography (silica gel, petroleum/ethyl acetate eluent). Isolated yield based on the starting nitrile.
[c] E-form determined by ^1H NMR. All products gave satisfactory ^1H NMR, IR and MS data.

of benzaldehyde with an equimolar amount of malononitrile gave $PhCH=C(CN)_2$ in 80% yield. However, the substrates bearing bulky substituents at the α-position to methylene, such as phenylacetonitrile and 2-cyanopropionate, were not reactive. This indicates that the present reaction containing the cyano group would

TABLE 2. Polyhydrides catalyzed Knoevenagel reaction of **2** and ketones [a]

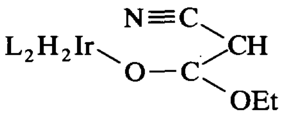
Entry	Ketones	Catalyst (mol%) [b]	Conv. (%) [c]	Yield (%) [d]	Products [e]	
1	 **3i**	**1A** (1.7) **1B** (1.2)	87 81	75 72		**4i**
2	 **3j**	**1A** (1.3) **1B** (0.9)	91 50	84 33		**4j**
3	 **3k**	**1A** (1.1) **1B** (1.0)		82 85		**4k**
4	 **3l**	**1A** (1.0)			No reaction	
5	$(CH_3)_2C=O$ **3m**	**1A** (1.1)		26	 $(CH_3)_2-C=C(CN)-COOEt$	**4m**
6	 $CH_3C(=O)CH_2CH_3$ **3n**	**1A**		30	 $CH_3CH_2-C(CH_3)=C(CN)-COOEt$	**4n** [f]

[a] Reacted in THF for 48 h. $[NCCH_2COOEt]/[Ketone]$ 1 : 1.2.
[b] **1A** = $IrH_5(^iPr_3P)_2$, T = 65°C; **1B** = $RuH_4(Ph_3P)_3$, T = 25°C.
[c] Determined by ^1H NMR.
[d] Isolated by column chromatography. Yield based on nitrile.
[e] All products gave satisfactory ^1H NMR, IR and MS data.
[f] *cis / trans* form was not determined.

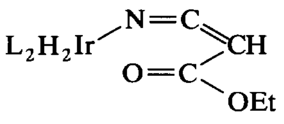
probably be distinguished from the aldol reaction mechanism in the presence of base or Lewis acid.

When alkene was added to a solution of ethyl cyanoacetate and Ir–polyhydride in THF, no insertion product of alkene into the metal–methine carbon bond was obtained. Thus a solution of $IrH_5(^iPr_3P)_2$ and $NCCH_2CO_2Et$ or manononitrile in $CDCl_3$ followed by aldehyde was determined by ^1H NMR spectrometry. The appearance of proton signals at 5.3, 4.6 and −22.2 ppm (triplet, $J = 15.3$ Hz) as well as the disappearance of the proton signal at 5.3 ppm after the aldehyde was added to the above solution indicate the presence of the hydrides bound to metal Ir and the generation of an intermediate of metal–enolate. This is coincident with Komiya's result that the active intermediate in the Ru-catalyzed aldol reaction did not involve any linkage between methine carbon and Ru but instead involved the coordination of the cyano group [4].

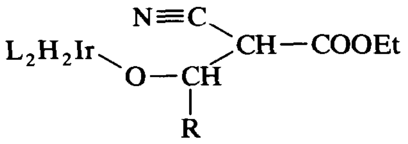
From the chemoselective reaction of nitriles and the results of NMR spectra, we suggest that the mechanism of the Knoevenagel reaction catalyzed by transition metal polyhydrides probably proceeds via oxidative addition of the active methylene C–H bond and it then may be rearranged to the intermediate **6** due to the coordination and tautomerization of the cyano group. The interconversion or an equilibrium between the metal–enolate and keteimine **7** would take place prior to the aldol-type addition to the carbonyl compounds (probably via intermediate **8**).



(**6**)



(**7**)



(**8**)

Other mechanisms proceed via protonation of the polyhydride by the acidic proton of methylene followed by coordination and rearrangement of the cyano group cannot be ruled out.

Transition metal polyhydride-mediated reactions can be carried out under very mild conditions due to the dissociation of the dihydrogen ligand as a facile leaving group leading to unsaturated metal complexes [6c,8]. The present catalytic reaction does not need a base and the products were (*E*)-α-cyano-α,β-unsaturated esters exclusively. This reveals the catalytic reactivity of transition metal polyhydrides in the C–C bond forming reaction.

2. Experimental details

All the reactions were carried out under prepurified nitrogen or argon using Schlenk techniques. The complexes **A** [9], **B** [10] and **C** [11] were prepared by published methods. The aldehydes were purchased from Tokyo Kasei or Aldrich Chemical Co and purified by distillation under nitrogen. ^1H NMR spectra were recorded on a Varian EM-360 or Varian XL-200 spectrometer. Chemical shifts (δ) were expressed in parts per million with Me_4Si as an internal standard. Infrared spectra were taken with a Shimadzu IR-440 instrument. Mass spectral data were obtained by electron ionization on a Finnigan 4021 GC/MS/DC instrument.

2.1. General procedure for the catalytic Knoevenagel condensation

A mixture of ethyl cyanoacetate (**2**) (3.0 mmol), aldehydes or ketones (**3**) (3.0 mmol) and catalyst (**1**) (0.03 mmol) in THF (1.0 cm^3) was heated at 65°C for 24 h. After cooling and removal of the solvent, the residue was isolated by column chromatography on silica gel (elution with petroleum/ethyl acetate). All products **4** or **5** were determined by ^1H NMR, IR and MS spectra.

*Ethyl 2-cyano-3-phenyl-2-propenoate (**4a**).* ν_{max} (Nujol/cm^{-1}) 2250(CN), 1720(C=O), 1600(C=C), 1195(C–O); ^1H NMR ($CDCl_3$, 200 MHz): δ8.26 (s, 1H); 8.01 (m, 2H); 7.53 (m, 3H); 4.40 (q, 2H); 1.40 (t, 3H). *m/z* 201 (M^+, 100%), 172, 156, 128, 102. Anal. Found: C, 71.30, H, 5.30, N, 6.69. $C_{12}H_{11}NO_2$ calc.: C, 71.64, H, 5.47, N, 6.97%.

*Ethyl 2-cyano-3-(4-methylphenyl)-2-propenoate (**4b**).* ν_{max}(Nujol/cm^{-1}) 2200(CN), 1725(C=O), 1600(C=C), 1190(C=O). ^1H NMR(CCl_4, 60 MHz): δ 8.08 (s, 1H); 7.87 (m, 2H); 7.25 (m, 2H); 4.33 (q, 2H); 2.32 (s, 3H); 1.40 (t, 3H). *m/z* 215 (M^+, 100%), 187, 170, 142, 115.

*Ethyl 2-cyano-3-(4-methoxyphenyl)-2-propenoate (**4c**).* ν_{max}(Nujol/cm^{-1}) 2200(CN), 1710(C=O), 1590(C=C), 1180(C–O). ^1H NMR($CDCl_3$, 90 MHz): δ 8.16 (s, 1H); 7.96 (m, 2H); 6.96 (m, 2H); 4.36 (q, 2H); 3.88 (s, 3H); 1.40 (t, 3H). *m/z* 231 (M^+, 100%), 203, 186, 158, 132.

*Ethyl 2-cyano-3-(4-chlorophenyl)-2-propenoate (**4d**).* ν_{max}(Nujol/cm^{-1}) 2200(CN), 1720(C=O), 1600(C=C), 1190(C–O). ^1H NMR(CCl_4, 60 MHZ): δ 8.10 (s, 1H);

7.93 (m, 2H); 7.45 (m, 2H); 4.30 (q, 2H); 1.41 (t, 3H). *m/z* 235 (M^+, 100%), 207, 190, 162, 136.

*Ethyl 2-cyano-3-(4-fluorophenyl)-2-propenoate (**4e**).* ν_{max}(Nujol/cm^{-1}) 2200(CN), 1700(C=O), 1600(C=C), 1200(C–O). ^{1}H NMR(CCl_4, 60 MHz): δ 8.15 (s, 1H); 8.00 (m, 2H); 7.20 (m, 2H); 4.34 (q, 2H); 1.40 (t, 3H). *m/z* 220 ($M^+ + 1$, 100%), 191, 174, 146, 120.

*Ethyl 2-cyano-3-(4-nitrophenyl)-2-propenoate (**4f**).* ν_{max}(Nujol/cm^{-1}) 2200(CN), 1720(C=O), 1610(C=C), 1510(N–O), 1320(C–N), 1200(C–O). ^{1}H NMR($CDCl_3$, 60 MHz): δ 8.35 (m, 2H); 8.23 (s, 1H); 8.08 (m, 2H); 4.37 (q, 2H); 1.33 (t, 3H). *m/z* 246 (M^+), 218(100%), 201, 173, 147.

*Benzylidenemalononitrile (**5a**).* ν_{max}(Nujol/cm^{-1}) 2200(CN), 1680(C=C). ^{1}H NMR(CCl_4, 60 MHz): δ 7.90 (m, 2H); 7.60 (s, 1H); 7.50 (m, 3H). *m/z* 154 (M^+, 100%), 127, 103, 77.

*4-Methoxybenzylidenemalononitrile (**5c**).* ν_{max} (Nujol/cm^{-1}) 2200(CN), 1600(C=C), 1190(C–O). ^{1}H NMR($CDCl_3$, 60 MHz): δ 3.85 (S, 3H); 8.03 (m, 2H); 7.90 (m, 2H); 7.65 (s, 1H). *m/z* 184 (M^+, 100%), 169, 157, 133, 107.

*Ethyl 2-cyano-3-isopropyl-2-propenoate (**4h**).* ν_{max} (neat/cm^{-1}) 2200(CN), 1720(C=O), 1630(C=C), 1180(C–O). ^{1}H NMR(CCl_4, 60 MHz): δ 7.50 (d, $J = 10$ Hz, 1H); 4.33 (q, 2H); 3.0 (m, 1H); 1.30 (m, 9H). *m/z* 168 ($M^+ + 1$, 100%), 140, 122, 94.

*Ethyl 2-cyano-5-phenyl-2,4-pentadienoate (**4g**).* ν_{max} (Nujol/cm^{-1}) 2250(CN), 1700(C=O), 1600(C=C). ^{1}H NMR($(CD_3)_2C{=}O$, 200 MHz): δ 8.17 (d, $J_{32} = 12$ Hz, 1H); 7.80 (m, 2H); 7.68 (d, $J_{21} = 16$ Hz, 1H); 7.52 (m, 3H); 7.32 (dd, $J_{23} = 12$ Hz, $J_{21} = 16$ Hz, 1H); 4.36 (q, 2H); 1.38 (t, 3H). *m/z* 227 (M^+), 199, 182, 154(100%), 127, 115.

*Ethyl 2-cyano-2-cyclohexylidene-acetate(**4i**).* ν_{max} (Nujol/cm^{-1}) 2200(CN), 1720(C=O), 1600(C=C), 1200(C–O). ^{1}H NMR(CCl_4, 60 MHz): δ 4.25 (q, 2H); 2.95 (t, 2H); 2.65 (t, 2H); 1.70 (m, 6H); 1.35 (t, 3H). *m/z* 193 (M^+), 165, 148, 137, 121(100%).

*Ethyl 2-cyano-2-cyclopentylidene-acetate(**4j**).* ν_{max} (Nujol/cm^{-1}) 2200(CN), 1725(C=O), 1610(C=C). ^{1}H NMR(CCl_4, 60 MHz): δ 4.25 (q, 2H); 2.95 (t, 2H); 2.80 (t, 2H); 1.85 (m, 4H); 1.35 (t, 3H). *m/z* 179 (M^+), 151, 134, 123(100%), 105.

*Ethyl 2-cyano-2-(4-methylcyclohexylidene)-acetate (**4k**).* ν_{max}(film/cm^{-1}) 2200(CN), 1730(C=O), 1600(C=C). ^{1}H NMR($CDCl_3$, 200 MHz): δ 4.20 (q, 2H); 3.80 (dq, $J_1 = 14$, $J_2 = 2$, 1H); 2.96 (dq, $J_1 = 14$, $J_2 = 2$, 1H); 2.3–1.7 (m, 7H); 1.27 (t, 3H); 0.88 (d, 3H). *m/z* 208 ($M^+ + 1$, 100%), 179, 162, 151, 135.

*Ethyl 2-cyano-3-methyl-2-butenoate(**4m**).* ν_{max}(film/cm^{-1}) 2200(CN), 1720(C≡O), 1600(C=C). ^{1}H NMR($CDCl_3$, 60 MHz): δ 4.25 (q, 2H); 2.40 (s, 3H); 2.30 (s, 3H); 1.35 (t, 3H). *m/z* 153 (M^+), 138, 124, 108(100%), 98.

Acknowledgement

The authors gratefully acknowledge financial support from the National Natural Science Foundation of China.

References

1 G. Jones, *Organic Reactions*, Vol. 15, Wiley, New York, 1967, p. 204.

2 T. Naota, H. Taki, M. Mizuno and S. I. Murahashi, *J. Am. Chem. Soc.*, *111* (1989) 5954.

3 S. Paganelli, A. Schionato and C. Botteghi, *Tetrahedron Lett.*, *32* (1991) 2807.

4 Y. Mizuho, N. Kasuga and S. Komiya, *Chem. Lett.*, (1991) 2127.

5 (a) Y. Lin, D. Ma and X. Lu, *Tetrahedron Lett.*, 28 (1987) 3115; (b) Y. Lin, X. Zhu and Y. Zhou, *J. Organomet. Chem.*, *429* (1992) 269; (c) D. Morton and D. J. Cole-Hamilton, *J. Chem. Soc., Chem. Commun.*, (1988) 1154.

6 (a) D. E. Jr. Linn and J. Halpern, *J. Am. Chem. Soc.*, 109 (1987) 2969; (b) D. Eisenstein and K. G. Caulton, *J. Am. Chem. Soc.*, *111* (1989) 2346; (c) Y. Lin and Y. Zhou, *J. Organomet. Chem.*, *381* (1990) 179; (d) C. Bianchini, E. Farnetti, P. Frediani, M. Graziani, M. Peruzzini and A. Dolo, *J. Chem. Soc., Chem. Commun.*, (1991) 1336.

7 (a) Y. Lin, D. Ma and X. Lu, *Acta Chim. Sin.*, *3* (1988) 272; (b) D. Ma and X. Lu, *Tetrahedron Lett.*, *30* (1989) 843; (c) D. Ma and X. Lu, *Tetrahedron Lett.*, *30* (1989) 2109.

8 D. G. Hamilton and R. H. Crabtree, *J. Am. Chem. Soc.*, *110* (1988) 4126.

9 M. G. Clerici, S. D. Gioacchino, F. Maspero, E. Perrotti and A. Zanobi, *J. Organomet. Chem.*, *84* (1975) 375.

10 R. O. Harris, N. K. Hota, L. Sadavoy and J. M. C. Yuen, *J. Organomet. Chem.*, *54* (1973) 259.

11 N. G. Connelly, J. A. K. Howard, J. L. Spencer and P. K. Woodley, *J. Chem. Soc., Dalton Trans.*, (1984) 2003.