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Reactions of unsaturated amides under hydroformylation conditions

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Abstract

N,N-diethyl methacrylamide (**1**) undergoes hydroformylation, followed by subsequent reactions, under "oxo" conditions involving use of $Rh_4(CO)_{12}$ or $Rh_4(CO)_{12}$ in the presence of (*R,R*)-Diop (Diop = {2,2-dimethyl-1,3-dioxolane-4,5-diylbis (methylene)}bis(diphenylphosphine)) as the catalyst precursor. The product first formed arises from formylation at the unsubstituted unsaturated carbon atom, and subsequently gives α-methyl-γ-butyrolactone (**1b**), *N,N*-diethyl 2-methyl-4-hydroxybutyramide (**1e**), and *N,N*-diethyl 1-methyl-3-(diethylamino)butyramide (**1f**). Hydrogenation of the substrate takes also place. The product distribution can be strongly influenced by the reactions conditions. For *N,N,N′,N′*-tetraethyl itacondiamide (**2**) under similar reactions conditions only hydrogenation and isomerization products are formed.

Introduction

The hydroformylation of nitrogen containing unsaturated substrates such as amides and imides has been intensively studied [1]. Some reports on the enantioselective hydroformylation of *N*-vinyl and *N*-allyl imides have appeared [2]. No information on the hydroformylation of amides or imides of unsaturated acids has yet been published to our knowledge [1].

We have been interested in the asymmetric hydroformylation of unsaturated esters, in which rather high optical yields were achieved [3]. As an extension of that study we have investigated the behaviour under hydroformylation conditions of *N,N*-diethyl methacrylamide (**1**) and *N,N,N′,N′*-tetraethyl itacondiamide (**2**) in the presence of chiral and achiral catalysts.

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Table 1

Products from *N,N*-diethyl methacrylamide **1** under hydroformylation conditions [a]

Catalyst precursor	Temperature (°C)	*P* [b] (bar)	Reaction time (h)	Conversion (%)	Yields of the isolated products (%) [c]					
					1a	**1b**	**1c**	**1d**	**1e**	**1f**
$Rh_4(CO)_{12}$	100	80	53	90	18	10	tr	–	24	16
$Rh_4(CO)_{12}$	130	300	26	100	24	24	–	–	tr	29
$Rh_4(CO)_{12}$/(−)-Diop	130	300	32	86	33	tr	44	tr	–	tr
$PtCl(SnCl_3)$[(−)-Diop]	130	300	50	10	tr	–	10	–	–	–

[a] 0.05 mmol catalyst, 15 mmol substrate, 35 ml toluene. [b] Equimolar hydrogen and carbon monoxide gas mixture. [c] **1a** = *N,N*-diethyl 2-methylpropionamide; **1b** = α-methyl-γ-butyrolactone; **1c** = *N,N*-diethyl 2-methyl-3-formylpropionamide; **1d** = *N,N*-diethyl 2-methyl-2-formylpropionamide, **1e** = *N,N*-diethyl 2-methyl-4-hydroxybutyramide; **1f** = *N,N*-diethyl 2-methyl-4-(diethylamino)butyramide (compare also Scheme 1). tr = traces.

Table 2

Products from *N,N,N′,N′*-tetraethyl itacondiamide **2** under hydroformylation conditions [a]

Catalyst precursor	Temperature (°C)	*P* [b] (bar)	Reaction time (h)	Conversion [c] (%)	Composition [d] of the product mixture (%)		
					2a	**2b**	**2c**
$HRh(CO)(PPh_3)_3$	100	80	36	0	–	–	–
$HRh(CO)(PPh_3)_3$	130	300	90	98	83	16	1
$Rh_4(CO)_{12}$/3(−)-Diop	130	300	250	96	64	34	2
$PtCl(SnCl_3)$[(−)-Diop]	100	100	123	0	–	–	–

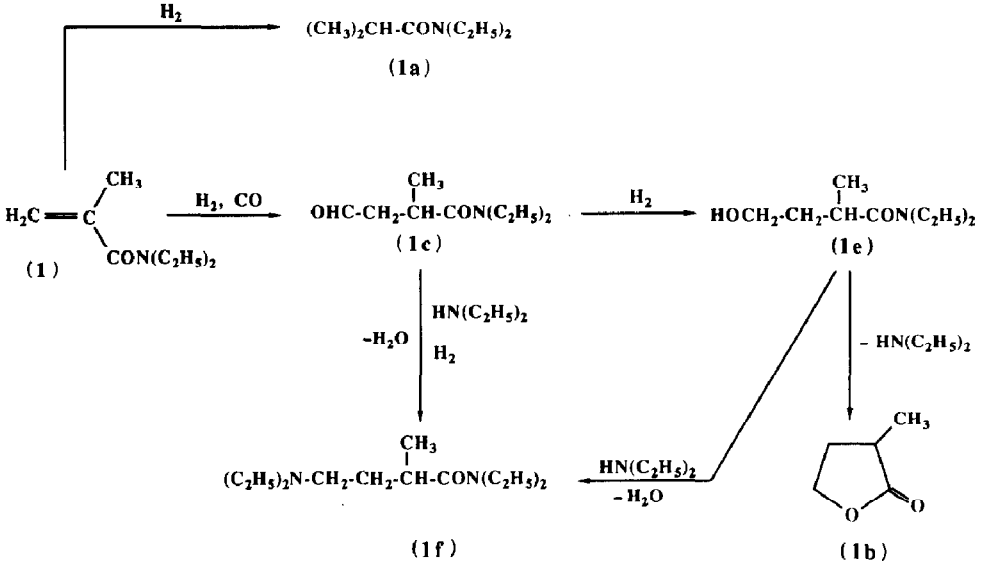
[a] 0.05 mmol catalyst, 15 mmol substrate, 35 ml toluene. [b] Equimolar hydrogen and carbon monoxide gas mixture. [c] Mol product ×100/mol substrate. [d] Determined by ^1H NMR. **2a** = *N,N,N′,N′*-tetraethyl methylsuccindiamide. **2b** = *N,N,N′,N′*-tetraethyl mesacondiamide; **2c** = *N,N,N′,N′*-tetraethyl citracondiamide.

Results and discussion

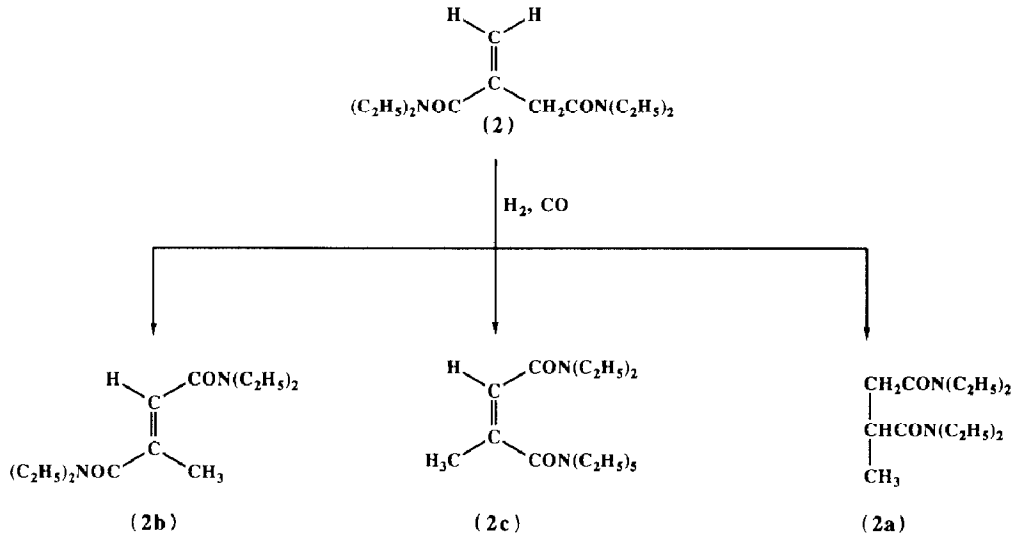
The hydroformylation of **1** (Table 1) under relatively mild conditions (80 bar of an equimolar mixture of hydrogen and carbon monoxide and 100 °C) gave only trace amounts of the expected regioisomer **1c** (Scheme 1), in which the formyl group has added to the unsubstituted unsaturated carbon atom, when $Rh_4(CO)_{12}$ was used as the catalyst precursor. Beside *N,N*-diethyl 2-methylpropionamide (**1a**, the product arising from hydrogenation of the substrate), three different compounds were identified, namely α-methyl-γ-butyrolactone (**1b**), *N,N*-diethyl-2-methyl-4-hydroxybutyramide (**1e**), and *N,N*-diethyl 2-methyl-4-(diethylamino) butyramide (**1f**). In a reaction carried out at higher temperature and pressure (130 °C and 300 bar of carbon monoxide and hydrogen) the hydroxy derivative **1e** practically disappeared and at the same time the amount of the other products increased. The hydroformylation product **1c** and the hydrogenation product **1a** were isolated from a reaction mixture obtained by using the same reaction conditions in the presence of $Rh_4(CO)_{12}$ modified in situ with (*R,R*)-Diop (Diop = {2,2-dimethyl-1,3-dioxolan-4,5-diylbis (methylene)}bis(diphenylphosphine)) [4] as the catalyst precursor. With this catalytic system the other products **1b** and **1f** and formed in only small amounts (less than 1% according to GC); furthermore the presence of traces of the alternative hydroformylation product *N,N*-diethyl 2-methyl-2-formylpropionamide (**1d**) was detected by linked GC-MS. Earlier studies [1b] have shown that the extent of hydrogenation of the formyl group is not increased when a rhodium–phosphine system is used as catalyst instead of the pure rhodium carbonyl.

Use of the $PtCl(SnCl_3)\{(R,R)$-Diop$\}$ [5] catalyst precursor, which was successfully used for the hydroformylation of unsaturated carboxylic esters [3], results in formation of **1c** and a trace amount of **1a**. The selectivity of this catalytic system appears to be good but its activity is rather low.

A possible route leading to the aforementioned products is presented in Scheme 1. Hydrogenation of the substrate (to give **1a**) and of the initially formed formyl



Scheme 1. Hydrogenation, hydroformylation, and subsequent reactions of *N,N*-diethyl methacrylamide under "oxo" conditions.



Scheme 2

product **1c** (to give **1e**) is possible under hydroformylation conditions [1b]. Elimination of $HN(C_2H_5)_2$ from **1e** would eventually lead to the cyclization product **1b**. The formed diethylamine could give **1f** through one or both of two pathways: (i) reaction with **1c** and subsequent hydrogenation of the intermediate enamine, and (ii) direct reaction with **1e** with elimination of water.

N,N,N',N'-Tetraethyl itacondiamide (**2**) does not undergo any hydroformylation under "oxo" conditions in the presence of rhodium catalyst precursors (Table 2 and Scheme 2), only hydrogenation (with formation of **2b**) and isomerization of the substrate take place. The extent of isomerization to the diamides of mesaconic acid and of citraconic acid (**2b** and **2c**, respectively) is even larger than in the previously reported case of dimethyl itaconate [6]. The extent of isomerization is higher with Diop instead of triphenylphosphine as the ligand. The hydrogenation of **2** to **2a** is enantioselective, but the optical yield is small (about 2.5%). The enantiomeric excess and the relationship between sign of the optical rotation and absolute configuration {(−)(*S*)} were determined through hydrolysis with phosphoric acid [7] to give methylsuccinic acid of known absolute configuration.

Experimental

General and instrumental

$Rh_4(CO)_{13}$ was synthesized from $[Rh(CO)_2Cl]_2$ as previously described [8], as was (*R,R*)-Diop [4,9]. $PtCl(SnCl_3)\{(R,R)$-Diop$\}$ was obtained from $PtCl_2$ (Johnson–Matthey Chemical Limited) by a procedure [5] in which $PtCl_2(PhCN)_2$ is treated with (*R,R*)-Diop to give $PtCl_2\{(R,R)$-Diop$\}$, which is then treated with $SnCl_2$ (Fluka product).

Toluene was distilled under nitrogen from sodium–potassium alloy in the presence of benzophenone.

The NMR spectra were recorded on a Bruker AM 300 WE spectrometer with tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin Elmer Polarimeter 141. Mass spectra were run on a Hitachi/Perkin Elmer RMU-6L spectrometer. GC analyses were carried out with a Perkin Elmer 990 or a

Perkin Elmer Sigma 4 chromatographs equipped with a flame ionization detector.

Quantitative analysis of the composition of the product mixture from *N,N,N',N'*-tetraethyl itacondiamide was carried out by ^{1}H-NMR spectroscopy involving the resonances (in C_6D_6) at 6.00 ppm (**2b**), at 5.65 ppm (**2c**), at 5.00 and 5.10 ppm (**2**) and at 2.00 ppm (**2a**).

Preparation of N,N-diethyl methacrylamide (1). Methacryloyl chloride was prepared from methacrylic acid [10] and added dropwise at −78°C to a toluene solution containing two equivalents of diethylamine. The red mixture thus obtained was filtered through Celite and the solvent was evaporated. The residue was distilled at 47–49°C/0.5 Torr.

Preparation of N,N,N',N'-tetraethyl itacondiamide (2). This compounds was prepared as reported above for *N,N*-diethyl methacrylamide starting from itaconyldichloride, which had been prepared from itaconic acid and phosphorus pentachloride [11]. The product was distilled at 124–128°C/0.5 Torr.

Reactions under hydroformylation conditions

In a typical experiment the solution of 9.4 mg (12.5×10^{-6} mol) of $Rh_4(CO)_{12}$ in 35 ml toluene was transferred under nitrogen into a 150 ml stainless steel autoclave which contained 7.1 g (0.05 mol) of *N,N*-diethyl methacrylamide. The autoclave was pressurized to the required pressure with an equimolar mixture of hydrogen and carbon monoxide and placed in an oil bath, which was then continuously shaked. The pressure was monitored throughout the reaction. After cooling and venting, the pale yellow solution was analyzed by linked GC-MS and then distilled for further characterization.

Characterization of the reaction products

N,N-Diethyl 2-methylpropionamide (1a). The hydrogenation product from **1** was separated by fractional distillation at 45–46°C/0.5 Torr. ^{1}H NMR ($CDCl_3$); 3.37 (q, 2H, $CON(CH_2^a)$, *J* 7.1 Hz); 3.33 (q, 2H, $CON(CH_2^b)$, *J* 7.1 Hz); 2.74 (h, 1H, $(CH_3)_2CH$, *J* 6.7 Hz); 1.18 (t, 3H, $CON(CH_2CH_3^a)$, *J* 7.1 Hz); 1.12 (d, 6H, $(CH_3)_2CH$, *J* 6.7 Hz); 1.10 (t, 3H, $CON(CH_2CH_3^b)$, *J* 7.1 Hz. ^{13}C-NMR ($CDCl_3$): 176.5 (*C*ON); 41.5 (NCH_2^a); 39.8 (NCH_2^b); 30.5 (*C*HCON); 19.5 ($(CH_3)_2CH$); 14.6 ($NCH_2CH_3^a$); 12.8 ($NCH_2CH_3^b$). MS (*m/z* rel. int.): 143/1000 (M^+); 100/980 ($CON(C_2H_5)_2$); 72/780 ($N(C_2H_5)_2$); 59/900 ($N(CH_3)(CH_2CH_3)$); 43/480 ($(CH_3)_2CH$).

α-Methyl-γ-butirolactone (1b). This product was separated and identified in an equimolar mixture with **1a** by comparison with an authentic material. ^{1}H-NMR ($CDCl_3$): 4.35 (ddd, 1H, OCH_2^a, *J* 2.7, 8.6, and 9.0 Hz); 4.19 (ddd, 1H, OCH_2^b, *J* 6.5, 9.0, and 9.8 Hz); 2.61 (ddq, 1H, $CHCH_3$, *J* 8.7, 7.1, and 10.3 Hz); 2.45 (m, 1H, $CHCH_2^a$); 1.93 (m, $CHCH_2^b$); 1.29 (d, 3H, $CHCH_3$, *J* 7.1 Hz). ^{13}C-NMR ($CDCl_3$): 179.7 (*C*OO); 66.0 (OCH_2); 33.8 (*C*HCH$_3$); 29.7 (CH_2CH); 14.9 (CH_3CH). MS (m/z/rel. int.): 100/35 (M^+); 56/550 ($(CH_2)_2CHCH_3$); 41/1000 ($(CH_2)_2CH$).

N,N-Diethyl 2-methyl-3-formylpropionamide (1c). This product was characterized after purification by fractional distillation. ^{1}H NMR (C_6D_6): 9.3 (t, 1H, *C*HO, *J* 0.6 Hz); 3.28 (dq, 1H, $N(CH_2^a)$, *J* 7.0 and 14.0 Hz); 3.07 (dq, 1H, $N(CH_2^b)$, *J* 7.0 and 14.0 Hz); 2.9 (ddd, 1H, CH_2^aCHO, *J* 18.0, 3.9, and 0.6 Hz); 2.80 (m, 3H, $CHCH_3 + N(CH_2)$); 1.80 (ddd, 1H, CH_2^bCHO, *J* 18, 3.9, and 0.6 Hz); 0.94 (t, 3H, CH_2CH_3, *J* 7 Hz); 0.89 (t, 3H, CH_2CH_3, *J* 7 Hz); 0.87 (d, 3H, CH_3CH, *J* 6.8 Hz).

^{13}C-NMR ($CDCl_3$): 201 (*C*HO); 174.3 (*C*ON); 48.2 ($CHOCH_2$), 42.0 and 40.4 ($N(CH_2)_2$); 30.3 ($CHCH_3$); 18.1 ($CHCH_3$); 14.6 and 13.0 ($N(CH_2CH_3)_2$).

*N,N-Diethyl 2-methyl-4-hydroxybutyramide (**1e**).* The hydrogenation product of **1c** was separated by fractional distillation at 108–110°C/0.5 Torr. ^{1}H NMR ($CDCl_3$): 3.65 (m, 2H, $HOCH_2$); 3.38 (q, 4H, $CON(CH_2)_2$, *J* 7.1 Hz); 2.91 (ddq, 1H, $CHCH_3$, *J* 8.1, 7.0, and 4.7 Hz); 2.6 (s, 1H, $HOCH_2$); 1.95 (dddd, 1H, CH_2^aCH); 1.69 (dddd, 1H, CH_2^bCH); 1.21 (t, 3H, CH_2CH_3, *J* 7.1 Hz); 1.16 (d, 3H, $CHCH_3$, *J* 6.9 Hz); 1.12 (t, 3H, CH_2CH_3, *J* 6.9 Hz). ^{13}C-NMR ($CDCl_3$): 176.3 (*C*ON); 59.7 ($HOCH_2$); 42.0 and 40.4 ($N(CH_2)_2$); 36.8 (CH_2CH); 32.1 (CH_2CH); 17.7 ($CHCH_3$); 14.7 and 12.9 ($N(CH_2CH_3)_2$).

*N,N-Diethyl 2-methyl-4-(diethylamino)butiramide (**1f**).* This product was separated and purified by fractional distillation at 112–113°C/0.5 Torr. ^{1}H NMR (C_6D_6): 3.32 and 3.20 (dq, 2H, $CON(CH_2)_2^{ab}$, *J* 7.2 and 14.2 Hz); 3.04 and 2.81 (dq, 2H, $CO(CH_2)_2^{cd}$, *J* 7.2 and 14.2 Hz); 2.65 (ddq, 1H, $CHCH_3$, *J* 5.5, 7.1, and 6.9 Hz); 2.4 (m, 2H, $(C_2H_5)_2NCH_2$); 2.39 (q, 2H, $CH_2N(CH_2)_2^{ab}$, *J* 7.1 Hz); 2.36 (q, 2H, $CH_2N(CH_2)_2^{cd}$, *J* 7.1 Hz); 2.12 (m, 1H, $CHCH_2^a$); 1.52 (m, 1H, $CHCH_2^b$); 1.15 (d, 3H, $CHCH_3$, *J* 6.9 Hz); 1.0 (t, 3H, $CONCH_2CH_3^a$, *J* 7.1 Hz); 0.94 (t, 6H, $CH_2N(CH_2CH_3)_2$, *J* 7.1 Hz); 0.84 (t, 3H, $CONCH_2CH_3^b$, *J* 7.1 Hz). ^{13}C-NMR ($CDCl_3$): 175.6 (*C*ON); 50.5 ($(CH_3CH_2)_2NCH_2$); 46.6 ($N(CH_2CH_3)_2$); 41.7 and 40.2 ($CONCH_2$); 33.2 ($CHCH_3$); 31.6 ($CHCH_2$); 18.1 ($CHCH_3$); 14.7 and 13.0 ($CON(CH_2CH_3)_2$); 11.6 ($CH_2N(CH_2CH_3)_2$). MS (*m/z*/rel. int.): 228/160 (M^+); 199/170 ($M - C_2H_5$); 156/550 ($M - N(CH_2CH_3)_2$); 100/1000 ($CO(NCH_2CH_3)_2$).

Methylsuccinic acid from N,N,N′,N′-tetramethyl methylsuccindiamide

1.6 g (6.6 mmol) of **2a** having $[\alpha]_D^{20} - 0.15$ (neat) were hydrolysed in phosphoric acid 50% [7]. The solution obtained was diluted with water and continuously extracted with diethyl ether. After evaporation of the solvent, methylsuccinic acid was isolated by distillation: $[\alpha]_D^{20} - 0.41$ (*c* 4.4 in ethanol). The optical purity was evaluated on the basis of the specific rotation reported for the optical pure (+)(*R*) acid [12] which is +16.5° under the same conditions.

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