A highly selective synthesis of 3-hydroxy-2-methylpropionamide involving a one-pot tandem hydroformylation–hydrogenation sequence†

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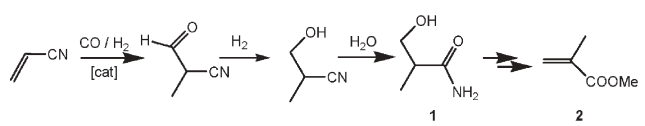
3-Hydroxy-2-methylpropionamide, an important intermediate in the synthesis of methyl methacrylate, has been obtained with excellent conversion and high selectivity from acrylamide by a tandem hydroformylation–hydrogenation sequence catalysed by Rh/PPh_3 and Raney Ni, respectively.

Methyl methacrylate is an important industrial product for preparing acrylic resins and custom plastics, among other products.[1] The industrial process for producing methyl methacrylate is the reaction of acetone with hydrogen cyanide to form the corresponding cyanohydrin, which is then transformed to methyl acrylamide and then esterified.[2] The problems of this process are associated with the handling of highly toxic HCN and the generation of high amounts of waste. Alternative high-performing processes are constantly being sought, one of them being through facile and highly selective catalytic routes. Methyl methacrylate can alternatively be obtained from 3-hydroxy-2-methylpropionamide (**1**, Scheme 1) by reaction with methyl formate. Compound **1**[3] can be obtained by hydroformylation of acrylonitrile with a Rh-based catalyst,[4] hydrogenation of the aldehyde and hydrolysis to the amide (Scheme 1). However, even with the best Rh/$P(OPh)_3$ catalytic systems, the selectivity (chemo- and regioselectivity) of the hydroformylation processes are not satisfactory. Thus, the selectivity in aldehydes can be up to 85% and the branched/linear product ratio >40 : 1.[4]

In this communication we report a highly selective new route to **1** which involves the hydroformylation of acrylamide **3**, an available and inexpensive substrate, and a subsequent hydrogenation step (Scheme 2). To our knowledge, the hydroformylation of acrylamide has yet to be reported. Tandem sequences, like the one described here, are becoming increasingly important in organic synthesis for the rapid preparation of high value compounds.[5]



Scheme 1 Synthesis of methyl methacrylate **2** starting from acrylonitrile.

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† Electronic Supplementary Information (ESI) available: Detailed spectroscopic data of **4b** and experimental procedures for the derivatization of **4b** to its dinitrophenylhydrazone derivative and to **1**. See DOI: 10.1039/b510813f

We started by studying the best conditions for the hydroformylation part of the tandem hydroformylation–hydrogenation sequence. So far, hydroformylation has been mainly investigated for simple olefinic hydrocarbons[6] and less so for functionalised substrates such as **3**. In recent years, however, great efforts have been made to hydroformylate functionalised substrates which are of interest for the synthesis of both chemical commodities and biologically-active compounds.[7] For example, unsaturated amides can be hydroformylated as a tool for the synthesis of α-amino-acids[8] and lactams.[9] Despite of this interest, few examples are known.[8,9] This is due to the difficulties of controlling simultaneously the chemo- and regioselectivity of the reaction for these kinds of substrate. These substrates are also prone to hydrogenation and polymerization under hydroformylation conditions.[9,10] For example, the hydroformylation of methacrylamide gives an equimolar mixture of hydrogenated and intramolecular condensation products, together with high amounts of polymerized material.[9]

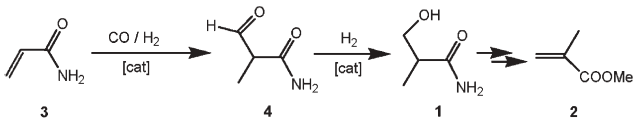
The Rh-catalyzed asymmetric hydroformylation of acrylamide **3** was initially tested with triphenylphosphite ($P(OPh)_3$). The catalysts were prepared *in situ* by adding the corresponding phosphite ligand to [Rh(acac)$(CO)_2$] as a catalyst precursor (0.6% molar ratio substrate/catalyst). The results are shown in Table 1.‡ At 70 °C and 95 atm CO/H_2 (1 : 1), the desired aldehyde **4b**[11] was obtained as the major product (Table 1, entry 1) in the ratio **4b/4l** of 93 : 7, with high activity. However 6% of propylamide (**5**), the product of hydrogenation reaction, and 7% of the dimerized product **6**[12] were also detected (Scheme 3).

We next studied the effect of several parameters (nature of the solvent, P/Rh ratio, temperature, CO/H_2 ratio and ligand) on the selectivity of the hydroformylation of acrylamide.

The results show that the efficiency of the process depended on the nature of the solvent (Table 1, entries 1–3). Acetonitrile (ACN) was found to be more regioselective for the branched aldehyde **4b** than THF, while DMF showed the highest regioselectivity but the lowest chemoselectivity (Table 1, entries 2 and 3).

A decrease in the P/Rh ratio has an extremely positive effect on the regioselectivity while the chemoselectivity was slightly lowered (Table 1, entry 4).

Varying the temperature had an important effect on both the chemo- and regioselectivity (Table 1, entries 1, 5–7). Increasing the

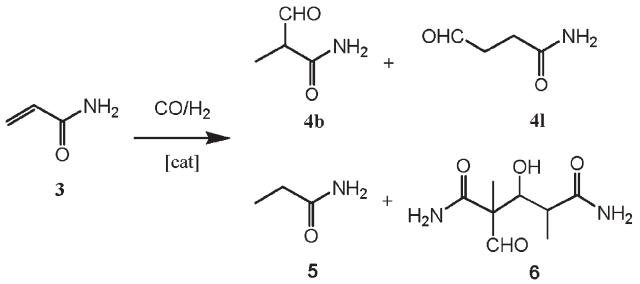


Scheme 2 New route for the synthesis of methyl methacrylate **2**.

Table 1 Hydroformylation of acrylamide **3** with $[Rh(acac)(CO)_2]$ and various ligands[a]

Entry	Ligand	T/°C	P/Rh	Solvent	% Conversion[b]	% Aldehyde (ratio **4b/4l**)[c]	% **5**[d]	% **6**[e]
1	$P(OPh)_3$	70	7 : 1	THF	100	87 (93 : 7)	6	7
2	$P(OPh)_3$	70	7 : 1	ACN	100	88 (98 : 2)	10	2
3	$P(OPh)_3$	70	7 : 1	DMF	100	74 (100 : 0)	16	10
4	$P(OPh)_3$	70	2 : 1	THF	100	83 (100 : 0)	15	2
5	$P(OPh)_3$	85	7 : 1	THF	100	86 (100 : 0)	10	4
6	$P(OPh)_3$	115	7 : 1	THF	100	77 (100 : 0)	6	17
7	$P(OPh)_3$	60	7 : 1	THF	80	75 (96 : 4)	2	3
8[f]	$P(OPh)_3$	70	7 : 1	THF	100	86 (93 : 7)	7	7
9	—	70	—	THF	0	—	—	—
10	PPh_3	70	7 : 1	THF	100	86 (100 : 0)	6	8
11	PPh_3	70	2 : 1	THF	99	70 (100 : 0)	19	11
12[g]	PPh_3	60	7 : 1	THF	100	97 (100 : 0)	3	0
13	PPh_3	115	7 : 1	THF	100	17 (100 : 0)	46	37

[a] Conditions: Total pressure P = 95 atm of CO/H_2 (1 : 1), substrate = 7 mmol, $[[Rh(acac)(CO)_2]]$ = 5.9×10^{-3} mol l^{-1}, 7.5 ml solvent, reaction time = 20 min. [b] Total conversion measured by GC using undecane as the internal standard. [c] Conversion into aldehydes measured by GC. Ratios of **4b** to **4l** measured by ^1H NMR. [d] Hydrogenation measured by GC. [e] Dimerization measured by GC. [f] P_{CO}/P_{H_2} = 2 : 1. [g] Isolated yield of **4b** was 93%.



Scheme 3 Hydroformylation of acrylamide **3**.

temperature had an extremely positive effect on regioselectivity (**4b/4l** ratio is >99) but the chemoselectivity decreased (Table 1, entry 1 *vs.* 5 and 6). Lowering the temperature to 60 °C had an extremely positive effect on both the regio- and chemoselectivity of the desired product **4b** (Table 1, entry 1 *vs.* 7). The best trade-off between chemo- and regioselectivity was therefore achieved at 60 °C.

In order to suppress the formation of hydrogenated product, we performed a hydroformylation experiment under a reduced H_2 partial pressure (Table 1, entry 8). However, the rate of hydrogenation *vs.* hydroformylation was not affected.

Reaction without ligand using $[Rh(acac)(CO)_2]$ did not proceed (Table 1, entry 9).

We next used triphenylphosphine as the ligand for the Rh-catalyzed hydroformylation of acrylamide **3**. Under the initial conditions (*i.e.* 70 °C, 95 atm of CO/H_2 (1 : 1), P/Rh = 7 : 1, THF solvent), the use of triphenylphosphine provided higher regioselectivity than the use of triphenylphosphite, while the chemoselectivity remained almost unaffected (Table 1, entries 1 *vs.* 10).

As previously observed with $P(OPh)_3$, the effect of lowering the P/Rh ratio decreased the chemoselectivity for aldehydes (Table 1, entries 10 *vs.* 11). As expected, lowering the temperature had a extremely positive effect on the chemoselectivity (Table 1, entries 10 and 13 *vs.* 12). Thus, the reaction carried out at 60 °C showed no condensation product combined with practically zero hydrogenation and excellent regioselectivity. However, further lowering of the temperature ($T \leqslant 50$ °C) has a dramatically negative effect on both conversion and selectivity, **5** being the major product.

Once the hydroformylation step was optimised, Raney Nickel (25% with respect to acrylamide) was added to the THF final reaction mixture without purification.§ The solution was pressurised to 95 atm and stirred for 20 h at 70 °C. GC analysis of the final solution showed that no **4b** was present and it was totally converted to 3-hydroxy-2-methylpropionamide (**1**).

The Pt/C system (25% with respect to acrylamide) in ethanol produced moderate conversion to **1** (up to 25% at 95 atm, 25 °C, 20 h). Other catalysts such Ru/C, $PtO_2/FeCl_2$ and Pd/C were not active under the conditions studied.

In summary, the tandem catalysed sequence hydroformylation/hydrogenation of acrylamide using $[Rh(acac)(CO)_2]/PPh_3$ and Raney Nickel allows alcohol **1** to be obtained with high selectivity and activity.

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Notes and references

‡ Standard hydroformylation experiments. In a typical hydroformylation experiment, a mixture of the acrylamide (7 mmol), $[Rh(acac)(CO)_2]$ (4.3×10^{-2} mmol), ligand (3.1×10^{-1} mmol, P/Rh = 7 : 1) and undecane (0.5 ml) (as GC internal standard) in 7.5 ml solvent was charged into a evacuated stainless steel autoclave. Then the reactor was pressurized up to 95 atm of syn-gas and heated to the convenient temperature. Stirring was initiated when thermal equilibrium had been reached. After 20 min, the reactor was cooled to room temperature and depressurised. Analyses of samples were performed by GC and NMR spectroscopy. **4b** was isolated by flash chromatography using AcOEt/MeOH (10 : 0.3) as eluent.

§ Standard hydrogenation experiments. In a typical hydrogenation experiment, to the final reaction mixture of the hydroformylation reaction of acrylamide was added the desired amount of catalyst. Then the reactor was then pressurized up to a suitable hydrogen pressure and heated to the appropriate temperature. Stirring was initiated when thermal equilibrium had been reached. After the appropriate reaction time, the reactor was cooled to room temperature and depressurised. Analyses of samples were performed by GC and NMR spectroscopy.

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11 The identity of aldehyde **4b** was confirmed by derivatization to the corresponding dinitrophenylhydrazone and to the alcohol **1** by reduction with sodium borohydride (see ESI†).

12 Product **6** was identified by GC-MS as mixture of four diastereoisomers, but they could not be isolated.