Supplementary Material (ESI) for Chemical Communications

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

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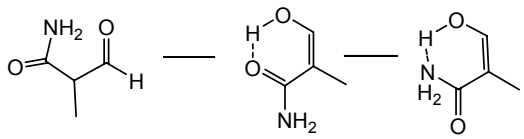
*Spectroscopy data of **4b***

4b is in equilibrium with the enolic forms **7** and **8** (Scheme 1) (identified by 2D NMR) and was characterised by GC-mass and NMR. These three species (**4b/7/8**) are present in different relative ratio according to the temperature of NMR experiments (34/40/26 at room temperature and 52/31/17 at 80°C). The enolic forms **7** and **8** disappeared when the NMR experiments were carried up in D_2O, as expected because this solvent can form hydrogen bonds with the aldehyde to prevent the formation of enolic forms.

4b: ^{1}H NMR (400 Hz, DMSO-d_6, 80ºC): δ 1.11 (d, 3H, J = 7.6 Hz), 3.35 (dq, 1H, J = 7.6 Hz, J = 1.2 Hz), 7.25 (br, 1H, NH), 7.60 (br, 1H, NH), 9.55 (d, 1H, J = 1.2 Hz). ^{13}C NMR (100.57 Hz, DMSO-d_6): 10.7, 52.7, 174.8, 200.3, IR (KBr, cm^{-1}): 3357, 3211 (ν(N-H)), 1726 ((ν(CO) aldehyde), 1660 ((ν(CO) amide). GC-MS (*m/z*): 101 (M^+), 73 (M^+-CHO), 57 (M^+-C(O)NH_2

7: ^{1}H NMR (400 Hz, DMSO-d_6, 80ºC): δ 1.55 (br, 3H, CH_3), 6.7 (br, 1H, NH), 7.00 (d, 1H, J = 10 Hz, CH=), 7.25 (br, 1H, NH), 13.8 (d, 1H, J = 9.9 Hz, -OH). ^{13}C NMR (100.57 Hz, DMSO-d_6): 12.9, 100.1, 159.0, 170.6.

8: ^{1}H NMR (400 Hz, DMSO-d_6, 80ºC): δ 1.60 (br, 3H, CH_3), 7.4 (br, 1H, CH=), 7.3 (m, 2H, NH_2), 9.7 (br, 1H, -OH). ^{13}C NMR (100.57 Hz, DMSO-d_6): 9.1, 106.1, 149.4, 170.9.



4b **7** **8**

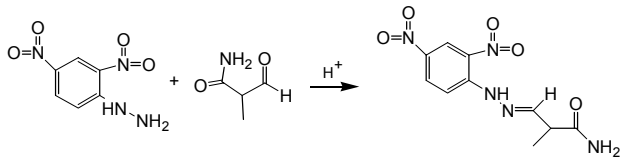
Scheme 1 Proposed keto-enolic equilibriums of the aldehyde **4b**

*Procedure for the derivatization of **4b** to the hydrazone **9** (Scheme 2).*[1]

2,4-dinitrophenylhydrazine (DNFH) (3g) was dissolved in 15 ml H_2SO_4 (conc.). Water (20 ml) and ethanol 95 % (75 ml) was added and the mixture was filtered off. 5 ml of the filtrate was added to a 5 ml of final reaction mixture obtained in the hydroformylation of acrylamide in THF (containing 88 % aldehyde). The mixture was stirred vigorously and cooled down to 4 ºC for 12h. An orange solid was formed, filtered off and recristalysed from ethanol. 0.3 g of orange product was obtained (80 % yield).

^{1}H NMR (400 Hz, DMSO-d_6, 80ºC): δ 1.27 (d, 3H, J = 10 Hz), 3.33 (m, 1H), 7.13 (br, 1H, NH), 7.56 (br, 1H, NH), 7.85 (d, 1H, J = 9.6 Hz), 8.05 (d, 1H, J = 6.0 Hz), 8.35 (dd, 1H, J = 9.6 Hz, J = 2.8 Hz), 8.82 (d, 1H, J = 2.8 Hz), 11.4 (br, 1H, NH-N). ^{13}C NMR (100.57 Hz, DMSO-d_6): δ 15.1, 43.4, 116.4, 123.1, 129.0, 129.8, 136.7, 144.8, 153.9, 173.3. Elemental Analysis ($C_{10}H_{11}N_5O_5$): Calculated: C, 42.71 %; H, 3.94 %; N, 24.90 %; Found: C, 42.50 %; H, 4.17 %; N, 24.15 %.

[1] J. Vilarrasa, in *Introducción al Análisis Orgánico*, ed. Universitaria de Barcelona, Barcelona, 1975, pp 97.



9

Scheme 2 Synthesis of 9.

*Procedure for the reduction of **4b** to **1**.*[2]

A solution of 15 ml of reaction mixture in THF was introduced into a three-necked flask equipped with a mechanical stirrer, a thermometer and an addition funnel. On the other hand, a solution of 543 mg of $NaBH_4$ (14.36 mmol), 2 ml NaOH 1N and 18 ml water was placed in the addition funnel. Then, the former solution was slowly added to the first one, with occasional cooling to keep the reaction at OºC. A small portion of the reaction mixture was treated with dilute sulphuric acid: if hydrogen was evolved the reaction was complete. After that, the solvent was removed with the rotavapor, and both 25 ml water and 15 ml HCl 1N was added. The mixture was washed with dichloromethane and ethyl acetate, and then the water was removed with the rotavapor. A few millilitres of methanol were added and an insoluble solid appeared which was filtered off. The solution was then concentrated and the alcohol **1** was precipitated with ether, filtered off and dried. The product was identified by NMR in DMSO, adulterated with traces of propionamide **5**.

^{1}H NMR (400 Hz, DMSO-d_6, 80ºC): δ 0.90 (d, 3H, J = 7.0 Hz), 2.30 (m, 1H), 3.25 (dd, 1H, J = 10.2 Hz, J = 6.2 Hz), 3.45 (dd, 1H, J = 10.2 Hz, J = 7.5 Hz) 4.75 (br, 1H, OH), 6.75 (br, 1H, NH), 7.24 (br, 1H, NH). ^{13}C NMR (100.57 Hz, DMSO-d_6): δ 14.3, 42.4, 63.8, 176.8.

[2] Spectroscopic data reported for **1**. R. A. Barrow, T. Hemscheidt, J. Liang, S. Paik, R. E. Moore, M. A. Tius., *J. Amer. Chem. Soc.*, **1995**, 117, 2479.