One-pot green synthesis of dihydropyran heterocycles

Supplementary Material

1. General Notes

This experiment aims provide the students with the knowledge about the *One-Pot* synthesis of dihydropyrans, specifically for the synthesis of 2-amino-4*H*-tetrahydropyran-3-carbonitrile **5a**. Aspects about the Multicomponent Reactions are also introduced. This general knowledge, will be applied in the synthesis of different derivatives by the employment of distinct aromatic aldehydes and/or 1,3-diketones. The purpose of preparing propargyl derivatives is to obtain compounds that can be functionalized in subsequent reactions, leading to the construction of more complex structures.

Regarding to the Experimental Procedure, is very important to maintain the reaction mixture under continuous and rigorous stirring for about 30-40 minutes before adding the 1,3-diketone. This step is probably responsible for the formation of the Knoevenagel-type intermediate (not isolated), necessary to subsequent steps (see Part 5, Discussion about the mechanism pathways, below).

All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (60F-254) visualizing with UV light or iodine. The isolation of product was made by a simple filtration under reduced pressure and washing the resulting solid with water and cold ethanol at temperatures around 5°C, since the product is partially solubilized at higher temperatures. The solid was dried in a desiccator under vacuum (with aid of a vacuum pump) and the melting points were determined on Olympus BX41 microscope equipped with Mettler-Toledo FP82HT hotplate equipment and are incorrect. The melting points of known compounds are provided in Table 1 for comparison.

The ^{1}H NMR and ^{13}C NMR spectra were recorded in a Varian-Inova 300 MHz and 75 MHz or Bruker 400 MHz and 100 MHz spectrometers, respectively. The samples were solubilized in DMSO-d_6, (hexadeutered dimethyl sulfoxide). The Chemical shifts (δ) are reported in ppm relative to DMSO-d_6 (at 2.50 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR). The multiplicity of signals was expressed as: *s* (singlet); *d* (doublet); *dd* (double doublet); *t* (triplet); *q* (quartet) and *m* (multiplet) and the coupling constants ^{3}J are expressed in hertz (Hz).

Caution: Note the ^{1}H NMR spectrum for the compound **5a** shows the signal of the solvent (at 2.50 ppm) superimposed on the signal of hydrogens of ketone ring moiety. It's worth noting too that the derivatives **5d, 5e and 5g** are described for the first time.

The IR spectra were recorded on a Varian 640-IR spectrometer and the results are expressed in cm^{-1} in the range of 4000-400 cm^{-1}.

A rationale for the involved mechanistic pathways in the multicomponent process is shown in Schemes 1 and 2, respectively (see part 4).

The synthetic protocol described here has been verified by a graduate student (Camila S. Santos) during their conclusion of the Monograph presented to Institute of Chemistry of the Universidade Federal do Rio Grande do Sul, as a part of her Final Examination to obtain the Bachelor degree in Chemistry. Each experiment was repeated, at least, two times and they were reproducible.

2. Notes of Laboratory of Session 1

Note 1. For the practical classes with periods of 3 hours, we suggest the reaction can be allowed to stir until the next day (24 hours or in a next Session), without prejudice to the yield of the final product. For example: reactions described in **Table 1**, should be carried out starting the experiment in a Laboratory Session 1 and finished in a Laboratory Session 2.

Note 2. For the synthesis of dihydropyrans **5b-e**, dimedone **3a** and the aldehydes **1b-e** were used instead **1a**. For the synthesis of dihydropyrans **5f,g**, aldehydes **1a** and **1e** were used, respectively. In these cases, were used the dimedone **3a** and 1,3-cyclohenedione **3b,** respectively, see **Table 1**. The molar ratio for the reactants remains the same for any reaction.

Note 3. To carry out the reaction, use a round bottom flask, stir bar, adapted with a stirrer plate. The reactional vessel can be closed with a rubber septa adapted with a cannula to equalize the possible internal pressures (Figure SM 4.2.5.1.1).

3. Notes of Laboratory of Session 2

Note 4. To filter the crude mixture, use a Buchner funnel coupled to a Kitasato flask connected to a vacuum pump to the forced filtration (Figures SM 4.2.5.1.2). The filtration process can be done with the aid of a glass rod (Figure SM 4.2.5.1.3).

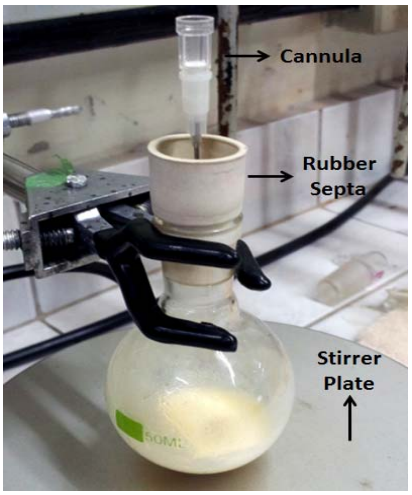


Figure SM 4.2.5.1.1

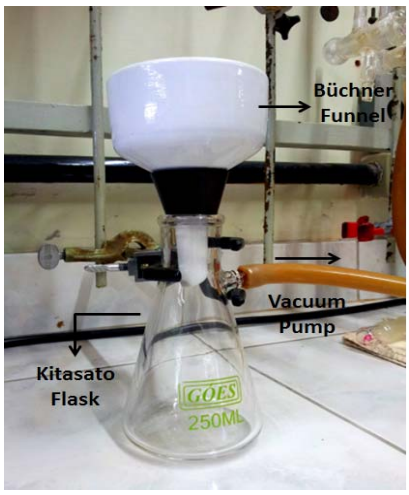


Figure SM 4.2.5.1.2

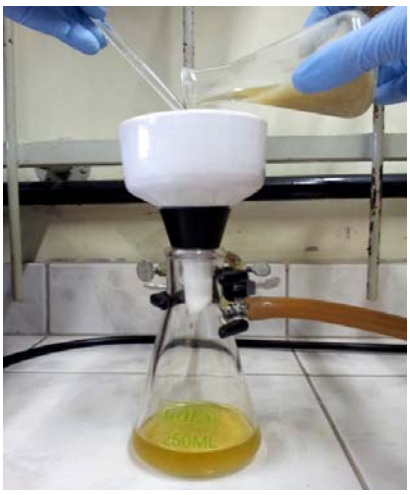


Figure SM 4.2.5.1.3

Note 5. Proceed this part in a fume hood.

Note 6. If necessary, the crude reaction mixture can be stored until the next session and then be filtered and dried.

4. Notes of Laboratory of Session 3

Note 7. The data of the obtained melting points can be compared with those reported in the appropriate literature, please, see **Table 1**.

Note 8. If an additional purification step is necessary for a more precise melting points or NMR spectra, the recrystallization of isolated solid can be made from hot ethanol and can be performed in an additional next *Session 4*. However, the careful washing with H_2O and cold ethanol are sufficient to obtain the products with a reasonable purity.

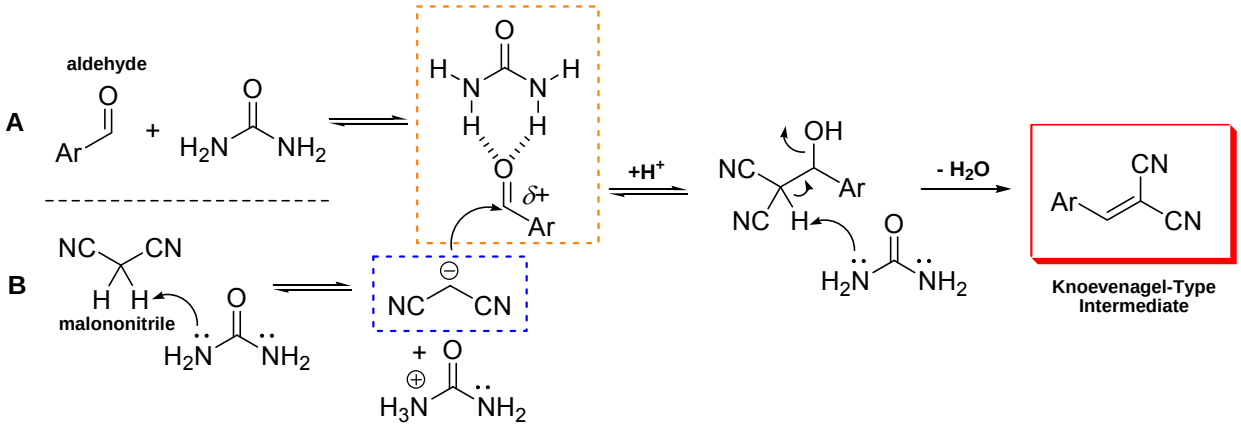
Note 9. Proceed the preparation of a sample with DMSO-*d6* in a fume hood. To safe handling, the use gloves and safety glasses are strongly encouraged.

5. Discussion about the mechanism pathways

First Step – Formation of Knoevenagel-type intermediate

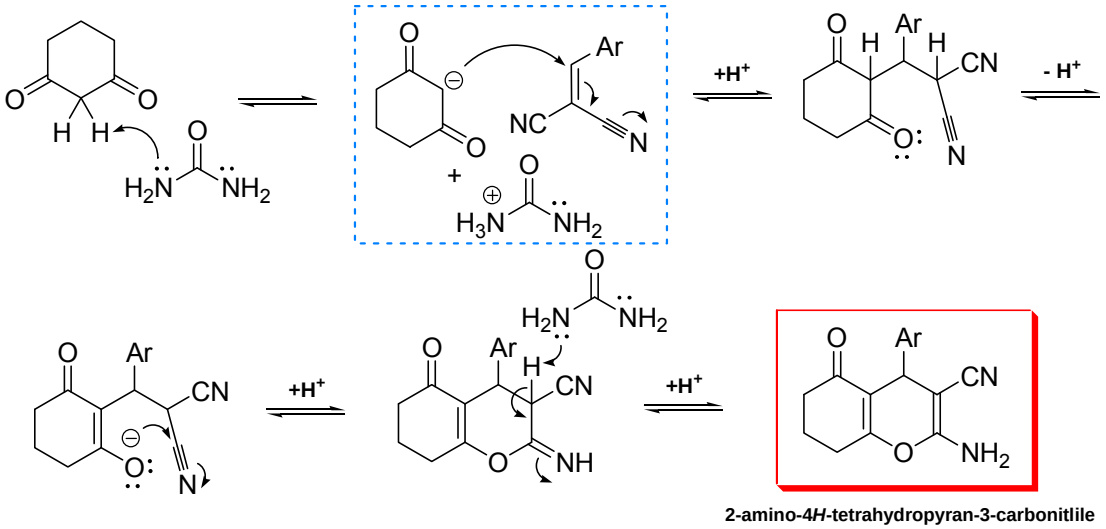
A - Activation of electrophile (aldehyde) through the double hydrogen bond formation.

B - Generation of the nucleophile by acid/base equilibria.



Scheme SM 4.2.5.1.1. Formation of the Knoevenagel-type adduct

Second Step - The Michael addiction reaction of 1,3-dicarbonyl compound and subsequent intramolecular cyclization leading to the target compound.



Scheme SM 4.2.5.1.2. Formation of 2-amino-4*H*-tetrahydro-pyran-3-carbonitrile derivatives

6. List of Chemical Structures of Compounds 5a-g

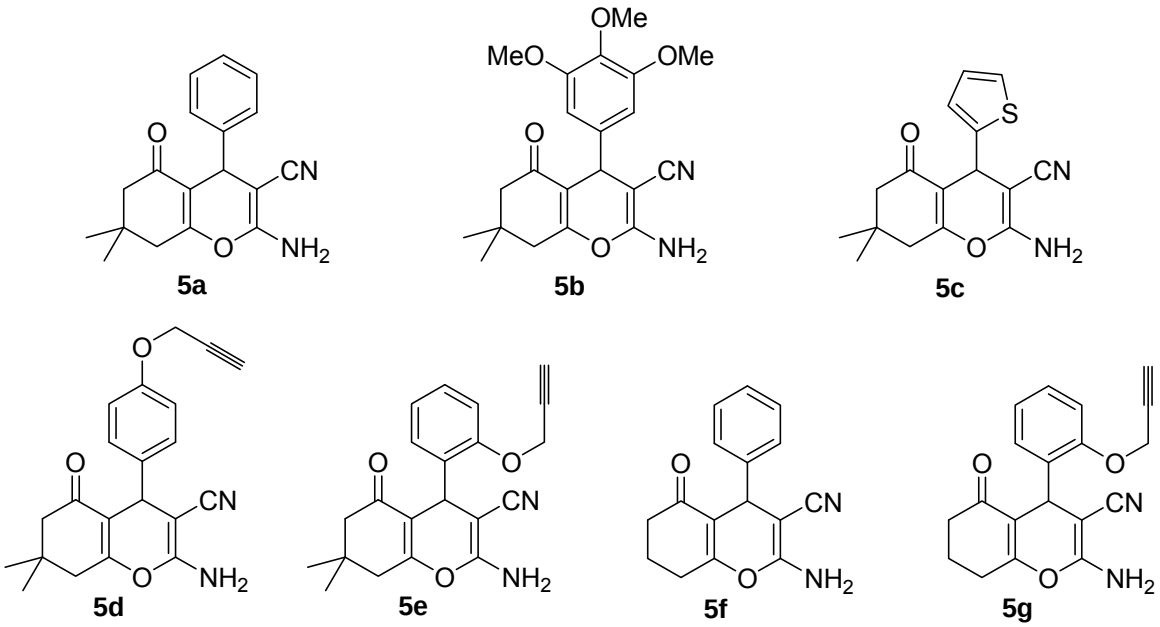


Figure SM 4.2.5.1.4. List of Chemical structures of ***5a-g***.

7. Table of results with others substrates

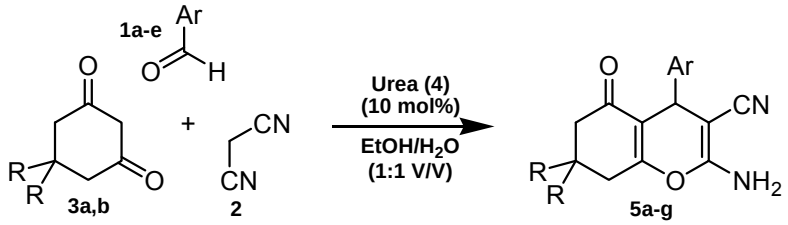


Table SM 4.2.5.1.1. *Synthesis de dyhydropiranes* ***5a-g*** *from aromatic aldeydes and 1,3-dicetonas.*

Entry		Aldehydes 1 (Ar)		Diketones 3 (R)	Time (h)[a]	5	Yield (%)[b]	M. P. (°C)[c]
1	**1a**	C_6H_5	**3a**	Me	4	**5a**	90	223-225[1]
2	**1b**	3,4,5-$(MeO)_3C_6H_2$	**3a**	Me	10	**5b**	75	180-183[2]
3	**1c**	2-Thiophene	**3a**	Me	3	**5c**	80	215-219[3]
4	**1d**	4-$(HCCCH_2O)C_6H_4$	**3a**	Me	10	**5d**	80	205-208
5	**1e**	2-$(HCCCH_2O)C_6H_4$	**3a**	Me	10	**5e**	70	204-207
6	**1a**	C_6H_5	**3b**	H	4	**5f**	96	210-214[4]
7	**1e**	2-$(HCCCH_2O)C_6H_4$	**3b**	H	10	**5g**	71	181-183

[a] See Note 1 - Notes of Laboratory Session 1.
[b] The yields refer to the best achieved value.
[c] The melting points are in accordance with the literature.

8. Characterization data of compunds 5a-g

8.1. Compound 5a:

2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile. White solid. M.p.: 222-225 °C.[1] ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm: 7.27 (m, 2H arom.), 7.16 (m, 3H, arom.), 7.00 (s, 2H, NH_2), 4.16 (s, 1H, -CH-Ph), 2.50 (*br.*s, 2H, -CH2-C=), 2.24 (d, *J* = 16.1 Hz, 1H, -CH-C=O), 2.08 (d, *J* = 16.1 Hz, 1H, -CH-C=O), 1.02 (s, 3H, $-CH_3$), 0.94 (s, 3H, $-CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ ppm: 196.1 (C=O), 162.9 (=C-NH_2), 158.9 (=C-O), 145.2 (C arom.), 128.8 (C arom.), 127.6 (C arom.), 127.0, 120.2 (-C≡N), 112.9 =<u>C</u>-C=O), 58.7 (=<u>C</u>-C≡N), 50.4 (<u>C</u>H_2-C=O), 39.6 (<u>C</u>H_2-C-), 36.0

[1] Fotouhi, L.; Heravi, M. M.; Fatehi, A.; Bakhtiari, K. *Tetrahedron Letters* **2007**, *48*, 5379-5381.

(CH-Ph), 32.8 (-C(CH$_3$)$_2$), 28.8 (-CH$_3$), 27.2 (-CH$_3$). I.R. ν cm^{-1}: 3390, 3319, 3209, 2962, 2356, 2199, 1737, 1677, 1657, 1604, 1554, 1413, 1370, 1342, 1248, 1214, 1160, 1036, 737, 695, 652.

***8.2. Compound 5b**:*

2-amino-4-(3,4,5-trimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile. White solid. M.p.: 180-181 °C.[2] ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 7.00 (s, 2H, NH$_2$), 6.39 (s, 2H arom.), 4.14 (s, 1H), 3.73 (s, 6H), 3.63 (s, 3H), 2.58-2.49 (m, 2H), 2.29 (d, *J* = 16.1 Hz, 1H), 2.15 (d, *J* = 16.1 Hz), 1.06 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm: 195.7, 162.8, 158.3, 152.7, 140.4, 136.1, 119.7, 112.3, 104.1, 59.9, 58.3, 55.7, 49.9, 39.0, 35.6, 28.6, 26.5. I.R. ν cm^{-1} 3395, 3302, 31783, 2934, 2833, 2189, 1644, 1505, 1457, 1417, 1389, 1320, 1245, 1211, 1120, 1034, 1005, 849, 775, 730, 656.

***8.3. Compound 5c**:*

2-amino-7,7-dimethyl-5-oxo-4-(thiophen-2-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile. White solid. M.p.: 216-218 °C.[3] ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm: 7.33 (dd, *J* = 5.0 and 1.2 Hz, 1H arom.), 7.14 (s, 2H, NH$_2$), 6.97 – 6.83 (m, 2H, arom.), 4.54 (s, 1H), 2.56 (d, *J* = 17.7 Hz, 1H), 2.43 (d, *J* = 17.7 Hz, 1H), 2.32 (d, *J* = 16.1 Hz), 2.16 (d, *J* = 16.1 Hz, 1H), 1.05 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ ppm: 195.0, 162.9, 159.3, 149.7, 127.3, 124.9, 124.5, 120.1, 113.4, 58.5, 50.3, 39.4, 32.2, 30.9, 29.1, 26.9. I.R. ν cm^{-1} 3374, 3319, 3204, 2964, 2879, 2198, 1676, 1658, 1602, 1417, 1389, 1357, 1246, 1214, 1151, 1036, 854, 699

***8.4. Compound 5d**:*

2-amino-7,7-dimethyl-5-oxo-4-[4-(prop-2-yn-1-yloxy)phenyl]-5,6,7,8-tetrahydro-4H-chromene-3-carbo nitrile. White solid. M.p.: 205-207 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ ppm: 7.07 (d, *J* = 8.8 Hz, 2H arom.), 6.99 (s, 2H, NH$_2$), 6.90 (d, *J* = 8.8 Hz arom.), 4.76 (d, *J* = 2.4 Hz, 2H), 4.14 (s, 1H), 3.56 (t, *J* = 2.4 Hz, 1H), 2.51 (s, 2H), 2.25 (d, *J* = 16.1 Hz), 2.11 (d, *J* = 16.1 Hz, 1H), 1.04 (s, 3H), 0.96 (s, 3H).

[2] Niknam, K.; Borazjani, N.; Rashidian, R.; Jamali, A. *Chinese J. Catal.* **2013**, *34*, 2245-2254.
[3] Hazeri, N.; Maghsoodlou, M. T.; Mir, F.; Kangani, M.; Saravani, H.; Molashahi, E. *Chinese J. Catal.* **2014**, *35*, 391-395.

^{13}C NMR (100 MHz, DMSO-d_6): δ ppm: 196.2, 162.7, 158.9, 156.4, 138.1, 128.7, 120.3, 115.0, 113.3, 79.7, 78.6, 58.9, 55.78, 50.5, 35.2, 32.3, 28.8, 27.3. I.R. ν cm^{-1} 3354, 3284, 3176, 2960, 2190, 1681, 1648, 1604, 1505, 1454, 1412, 1370, 1300, 1253, 1216, 1160, 1025, 976, 932, 847, 776, 714, 689, 652.

***8.5. Compound 5e**:*

2-amino-7,7-dimethyl-5-oxo-4-[2-(prop-2-yn-1-yloxy)phenyl]-5,6,7,8-tetrahydro-4H -chromene-3-carbo nitrile. White Solid. M.p.: 204-206 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 7.21-7.13 (m, 1H arom.), 7.08-6.99 (m, 2H arom.), 6.90 (m, 1H arom.), 6.84 (s, 2H, NH_2), 4.75 (dd, *J* = 16.0 and 2.4 Hz, 1H), 4.70 (dd, *J* = 16.0 and 2.4 Hz, 1H), 4.44 (s, 1H), 3.56 (t, *J* = 2.4 Hz, 1H), 2.53 (d, *J* = 16.1 Hz, 1H), 2.46 (d, *J* = 16.1Hz), 2.24 (d, *J* = 16.1 Hz, 1H), 2.06 (d, *J* = 16.1 Hz, 1H), 1.04 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm: 196.1, 163.5, 159.4, 155.6, 133.0, 129.6, 128.2, 121.5, 120.3, 113.3, 112.2, 79.8, 78.5, 57.6, 56.6, 50.5, 32.2, 29.0, 27.40. I.R. ν cm^{-1} 3460, 3323, 3248, 3183, 2194, 1681, 1657, 1598, 1492, 1458, 1414, 1369, 1295, 1259, 1215, 1144, 1121, 1022, 921, 858, 756, 703, 677, 644.

***8.6. Compound 5f**:*

2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile. White solid. M.p.: 205-207 ^{o}C.[4] ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.33-7.26 (m, 2H, arom.), 7.22-7.15 (m, 3H arom.), 7.02 (s, 2H, NH_2), 4.20 (s, 1H), 2.70-2.56 (m, 2H), 2.37-2.19 (m, 2H), 2.03-1.79 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ ppm: 196.3, 164.9, 158.9, 145.24, 128.8, 127.6, 127.0, 120.2, 114.2, 58.7, 36.8, 35.9, 26.9, 20.28. I.R. ν cm^{-1} 3321, 3171, 2192, 1719, 1684, 1651, 1603, 1657, 1453, 1417, 1294, 1261, 1175, 1135, 1066, 1001, 950, 892, 800, 765, 701, 640.

***8.7. Compound 5g**:*

2-amino-5-oxo-4-[2-(prop-2-yn-1-yloxy)phenyl]-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile. White solid. M.p.: 181-183 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.21-7.13 (m, 1H arom.), 7.05 (m, 2H

[4] Xu, J-C.; Li, W-M.; Zheng, H.; Lai, Y-F.; Zhang, P-F. *Tetrahedron* **2011**, *67*, 9582-9587.

arom.), 6.90 (m, 1H arom.), 6.84 (s, 2H, NH_2), 4.75 (d, *J* = 2.3 Hz, 2H), 4.46 (s, 1H), 3.56 (t, J = 2.3 Hz, 1H), 2.73-2.52 (m, 2H), 2.41-2.09 (m, 2H), 2.08-1.79 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 196.3, 165.4, 159.3, 155.6, 133.2, 129.4, 128.1, 121.6, 120.3, 113.5, 113.4, 80.0, 78.4, 57.7, 56.5, 36.9, 31.2, 27.0, 20.3. I.R. ν cm^{-1} 3384, 3286, 3201, 2191, 1740, 1682, 1650, 1606, 1491, 1458, 1408, 1294, 1263, 1210, 1170, 1136, 1115, 1066, 1003, 934, 860, 758, 682, 642.

9. Colection of ^{1}H NMR, ^{13}C NMR of compounds 5a-g.

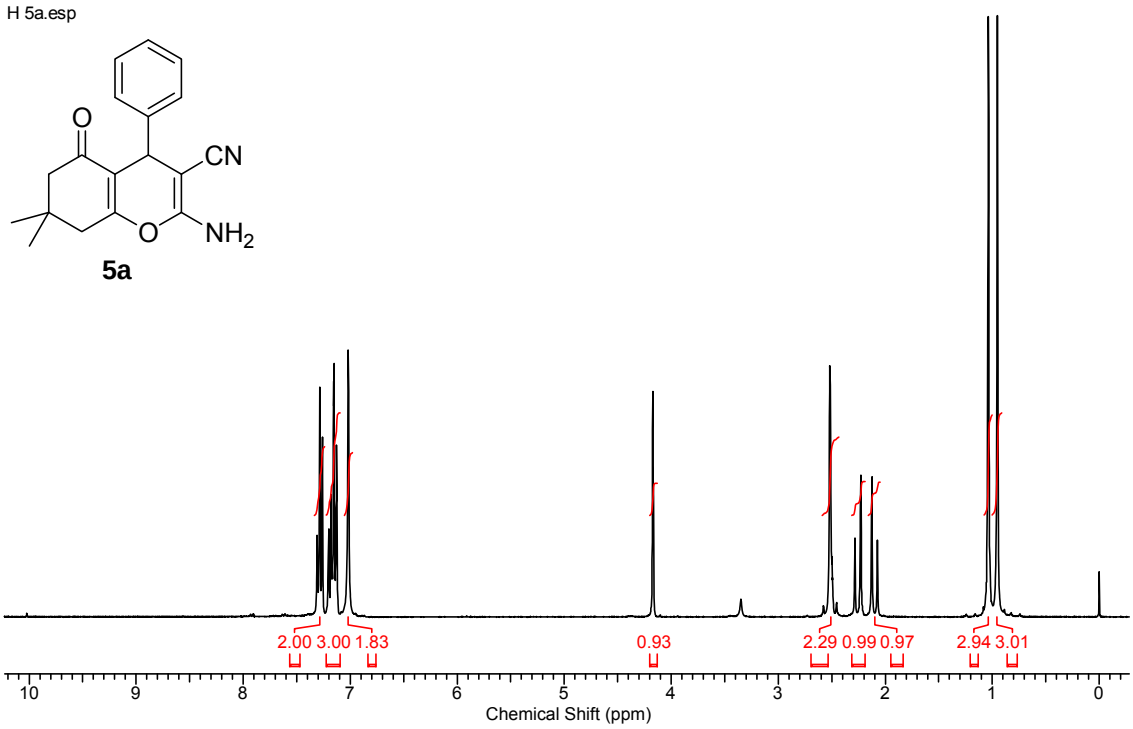


Figure SM 4.2.5.1.5.1. ^{1}H NMR (300 MHz, DMSO-d_6) of Compound ***5a***

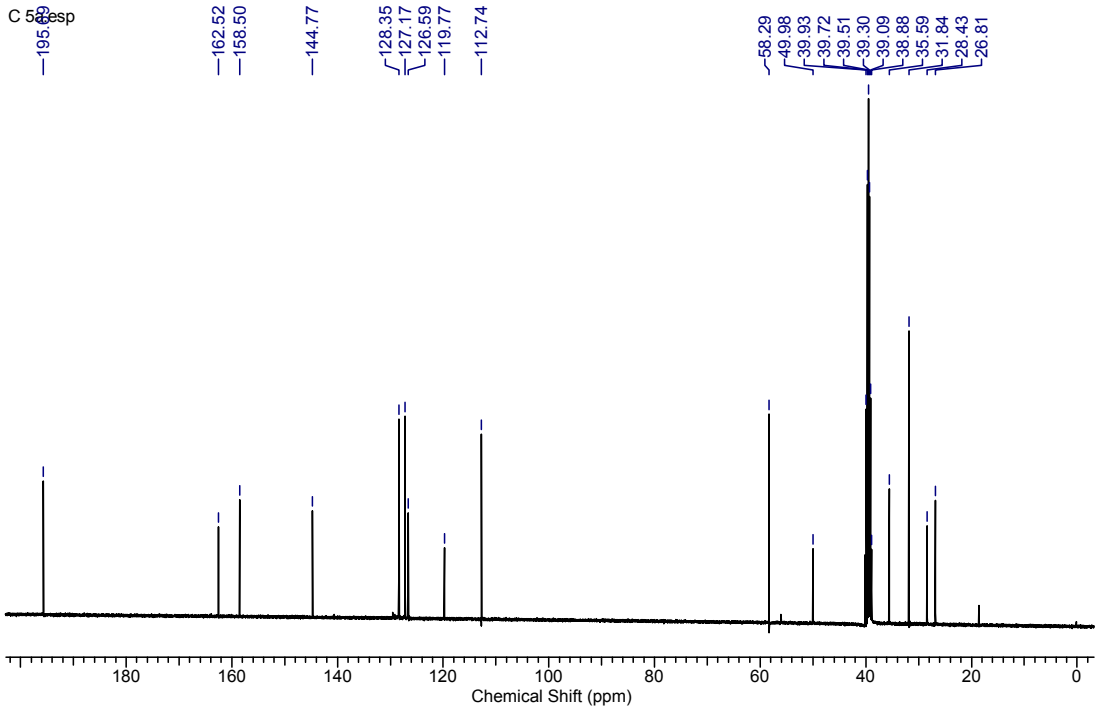


Figure SM 4.2.5.1.5.2. ^{13}C NMR (75 MHz, DMSO-d_6) do composto ***5a***.

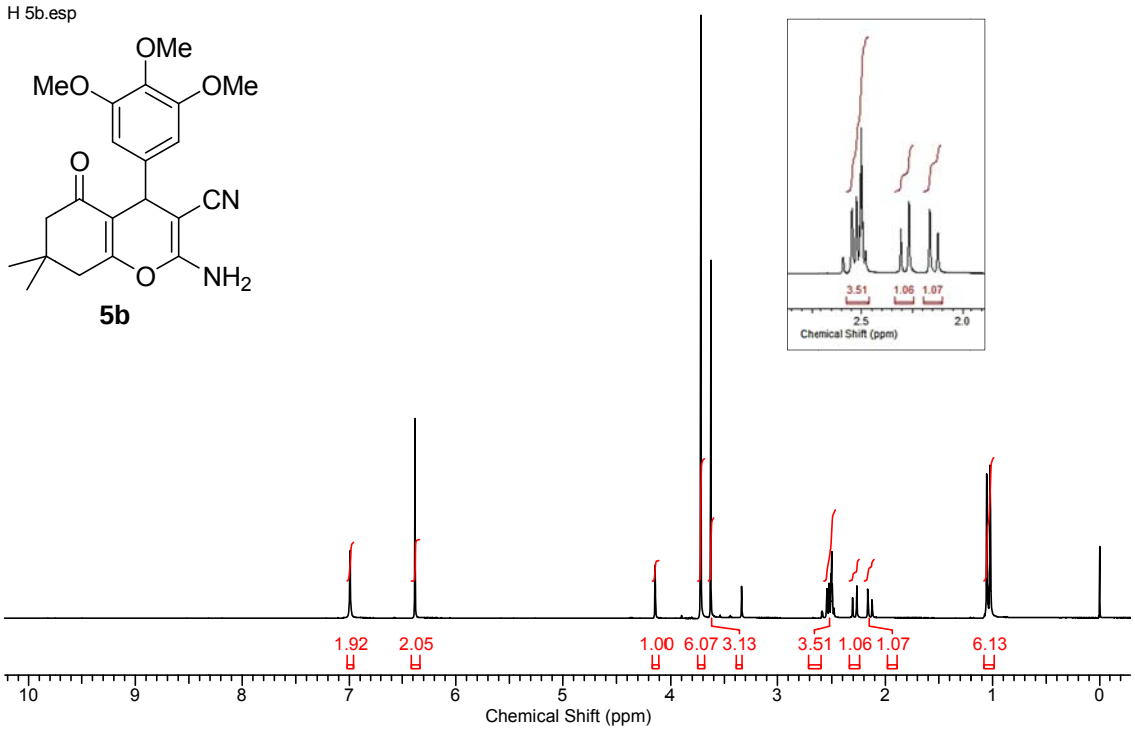


Figure SM 4.2.5.1.5.3. ^{1}H NMR (400 MHz, DMSO-d_6) of Compound ***5b***

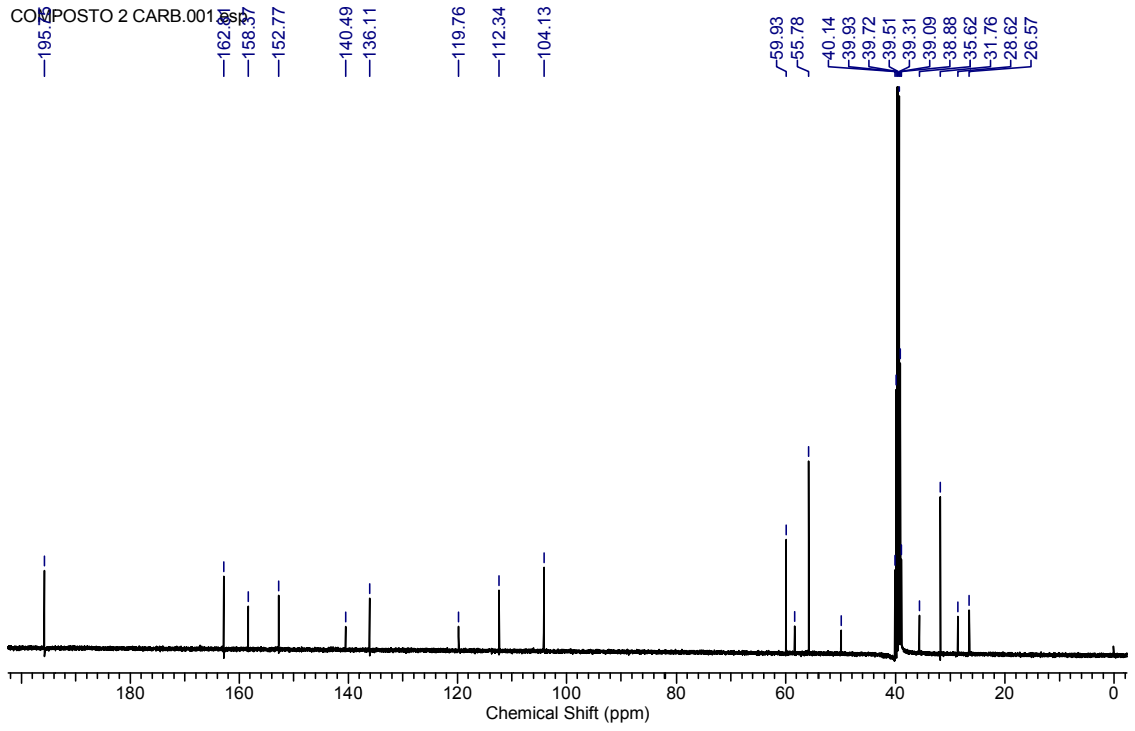


Figure SM 4.2.5.1.5.4. ^{13}C NMR (100 MHz, DMSO-d_6) of Compound ***5b***

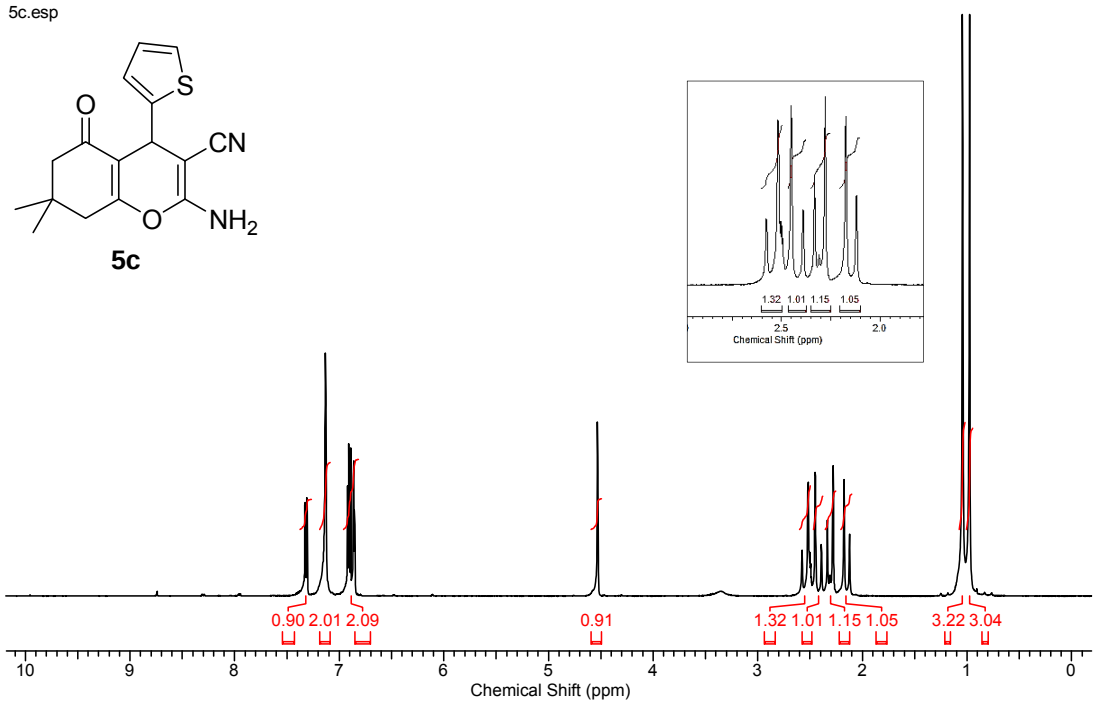


Figure SM 4.2.5.1.5.5. ^{1}H NMR (300 MHz, DMSO-d_6) of Compound ***5c***

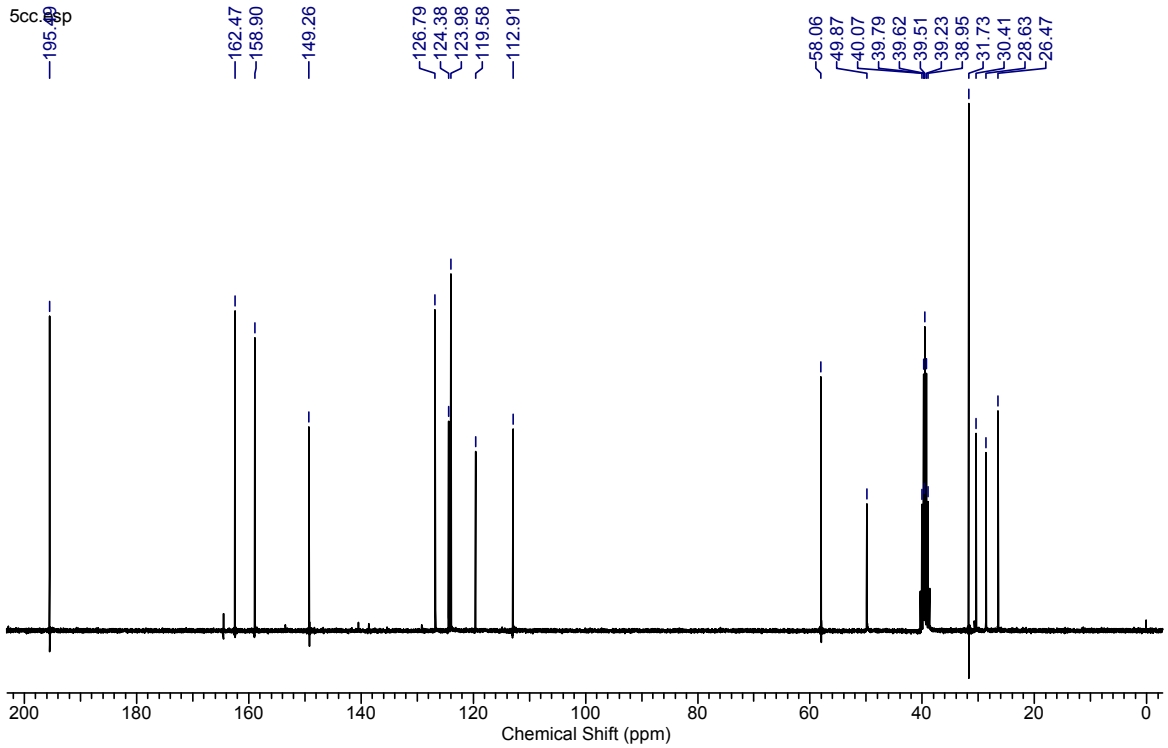


Figure SM 4.2.5.1.5.6. ^{13}C NMR (75 MHz, DMSO-d_6) do composto ***5c***.

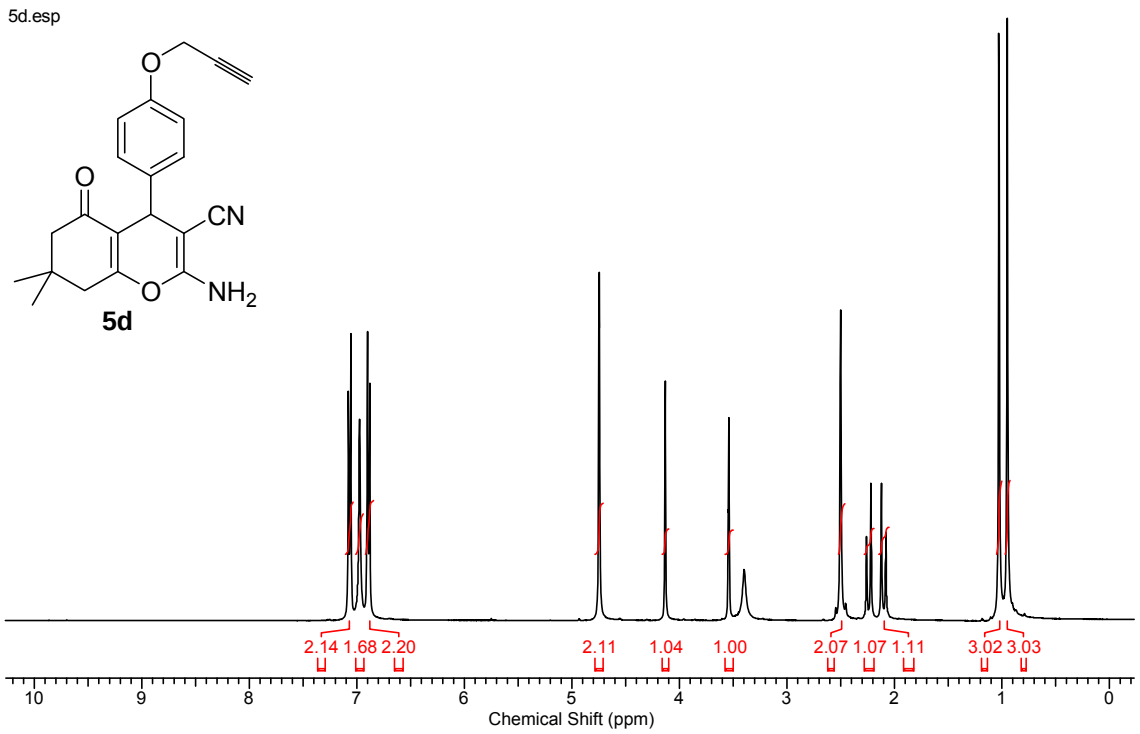


Figure SM 4.2.5.1.5.7. ^{1}H NMR (400 MHz, DMSO-d_6) of Compound ***5d***

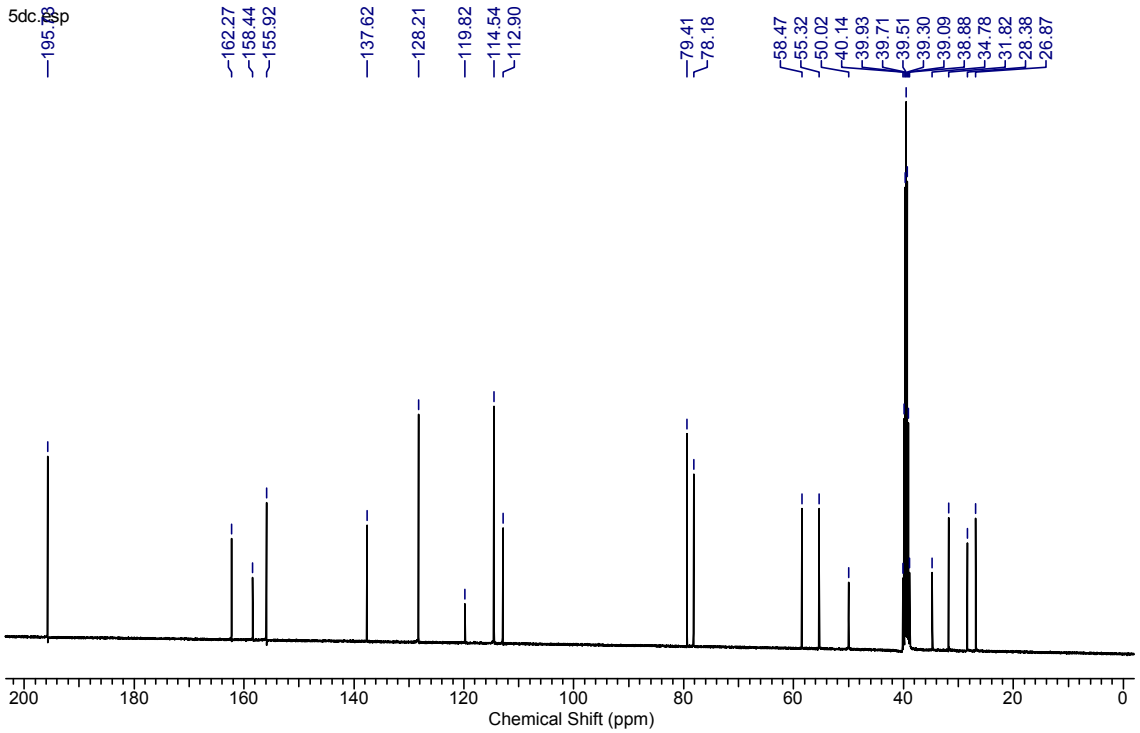


Figure SM 4.2.5.1.5.8. ^{13}C NMR (100 MHz, DMSO-d_6) of Compound ***5d***

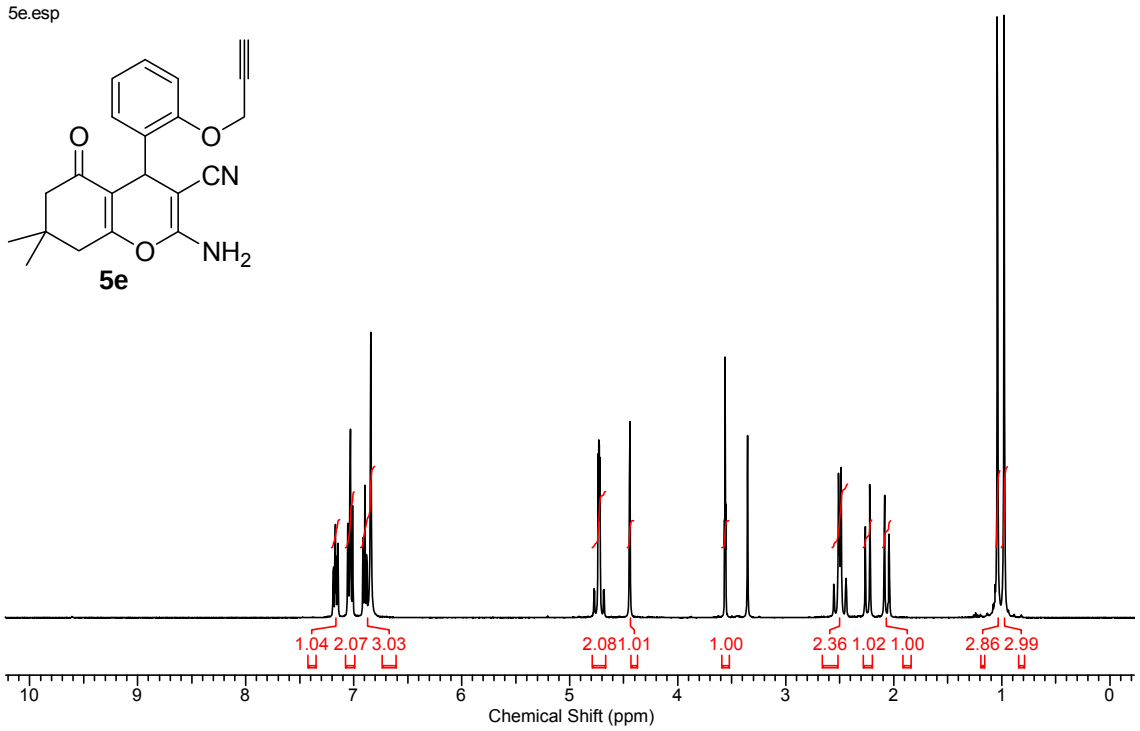


Figure SM 4.2.5.1.5.9. ^{1}H NMR (400 MHz, DMSO-d_6) of Compound ***5e***

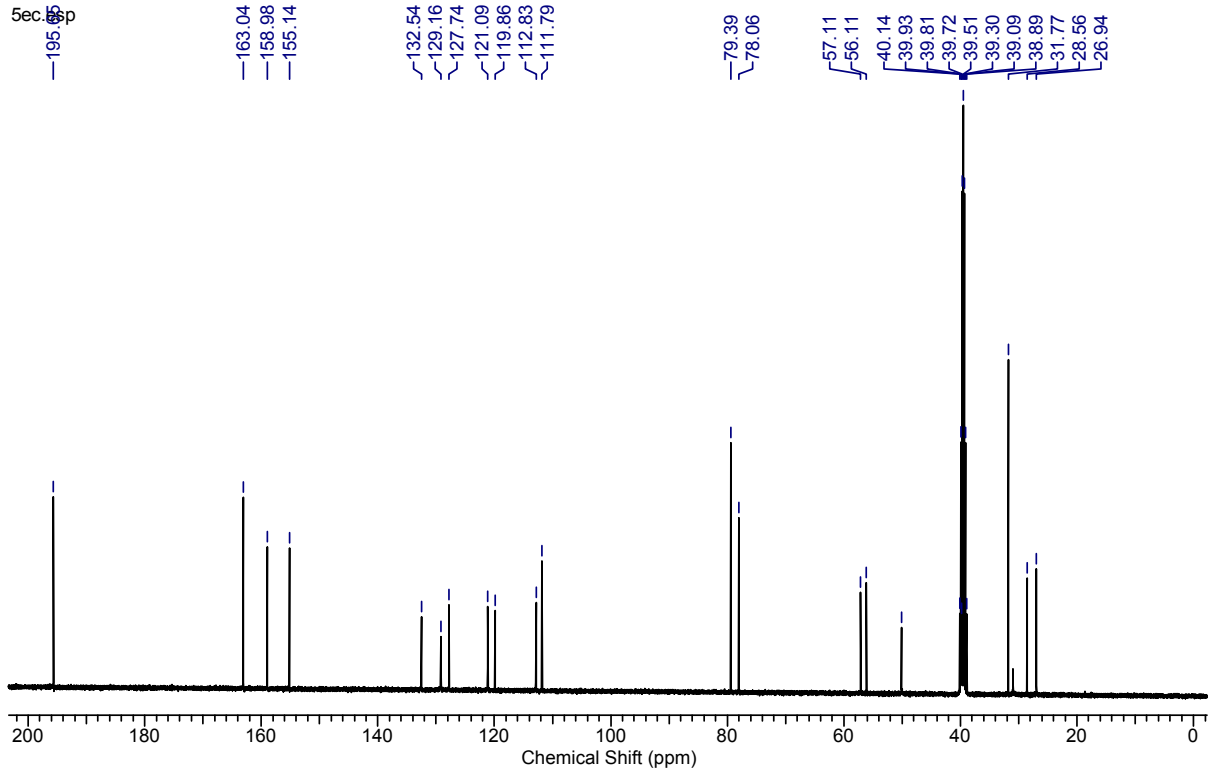


Figure SM 4.2.5.1.5.10. ^{13}C NMR (100 MHz, DMSO-d_6) of Compound ***5e***

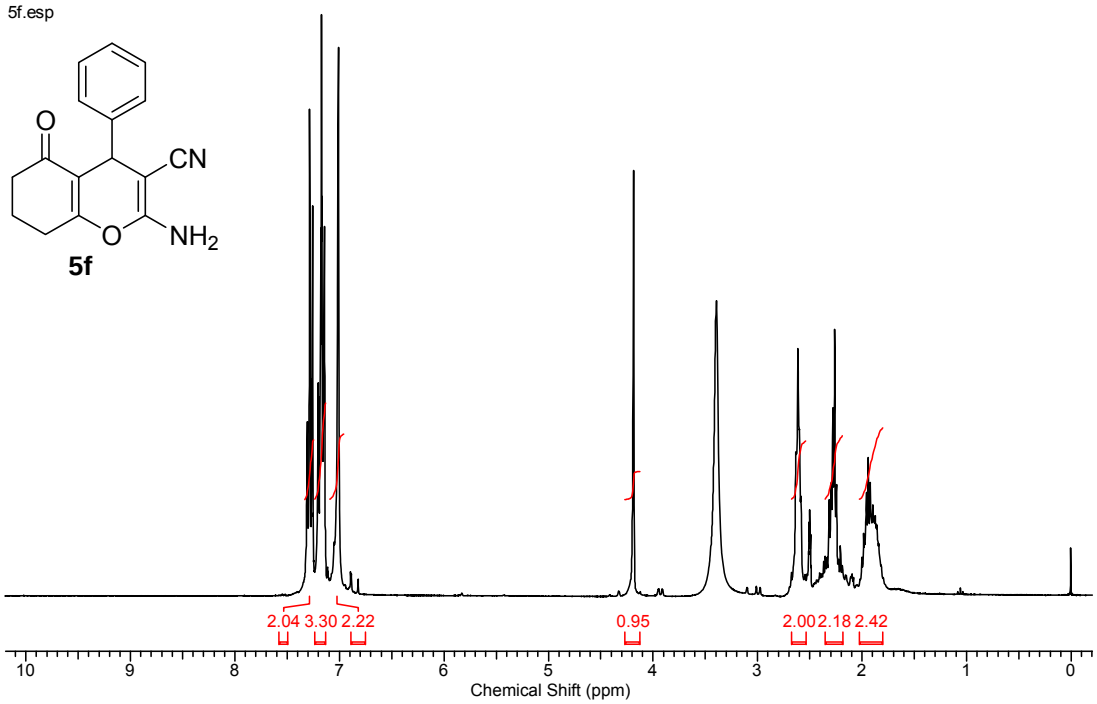


Figure SM 4.2.5.1.5.11. ^{1}H NMR (300 MHz, DMSO-d_6) of Compound ***5f***

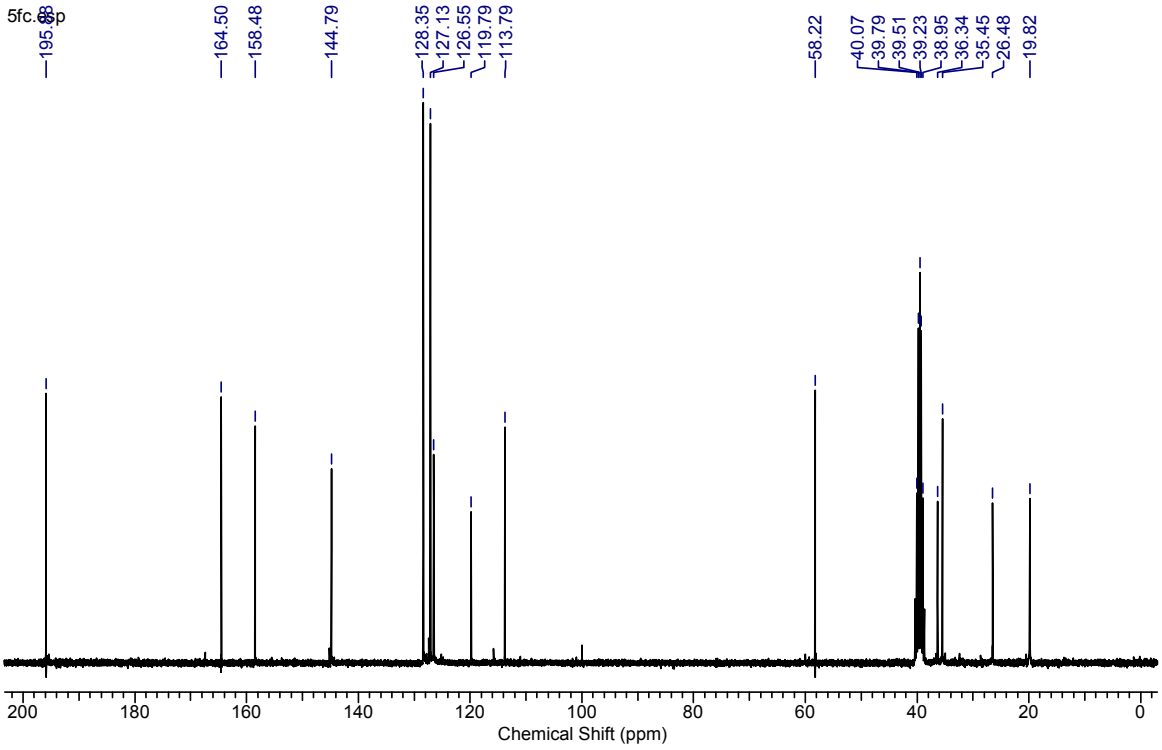


Figure SM 4.2.5.1.5.12. ^{1}H NMR (75 MHz, DMSO-d_6) of Compound ***5f***

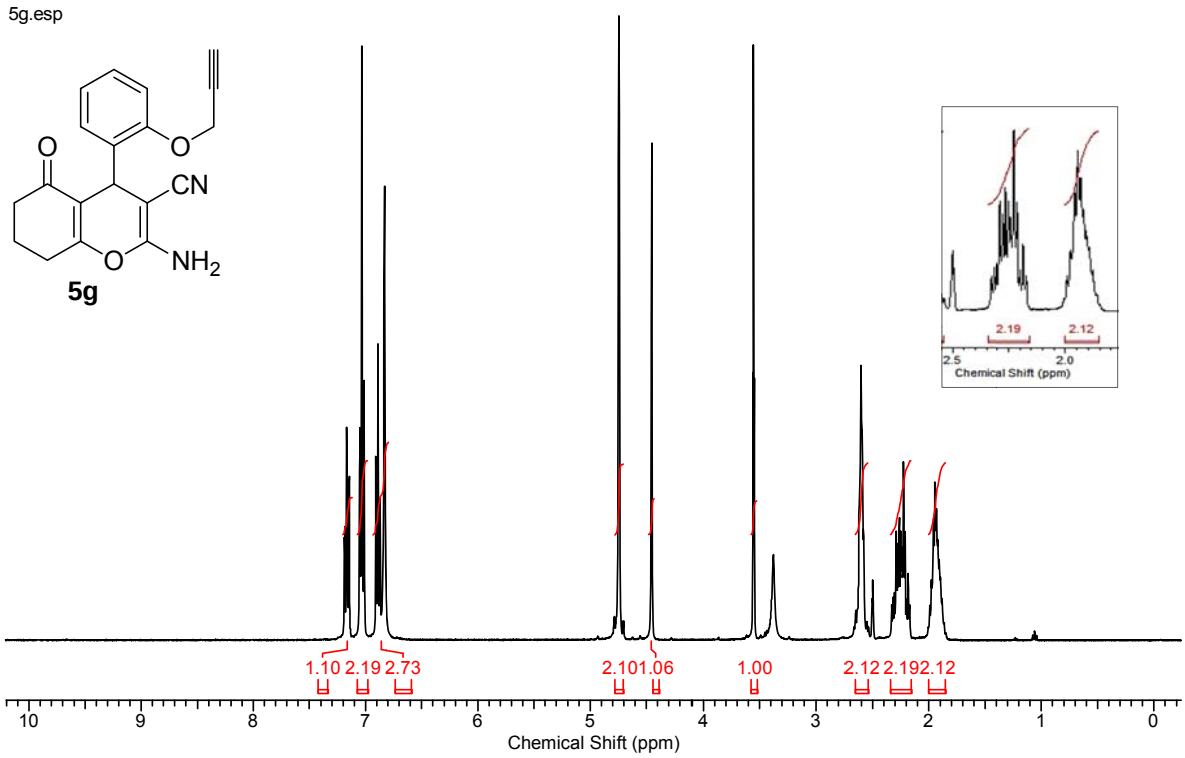


Figure SM 4.2.5.1.5.13. ^{1}H NMR (400 MHz, DMSO-d_6) of Compound ***5g***

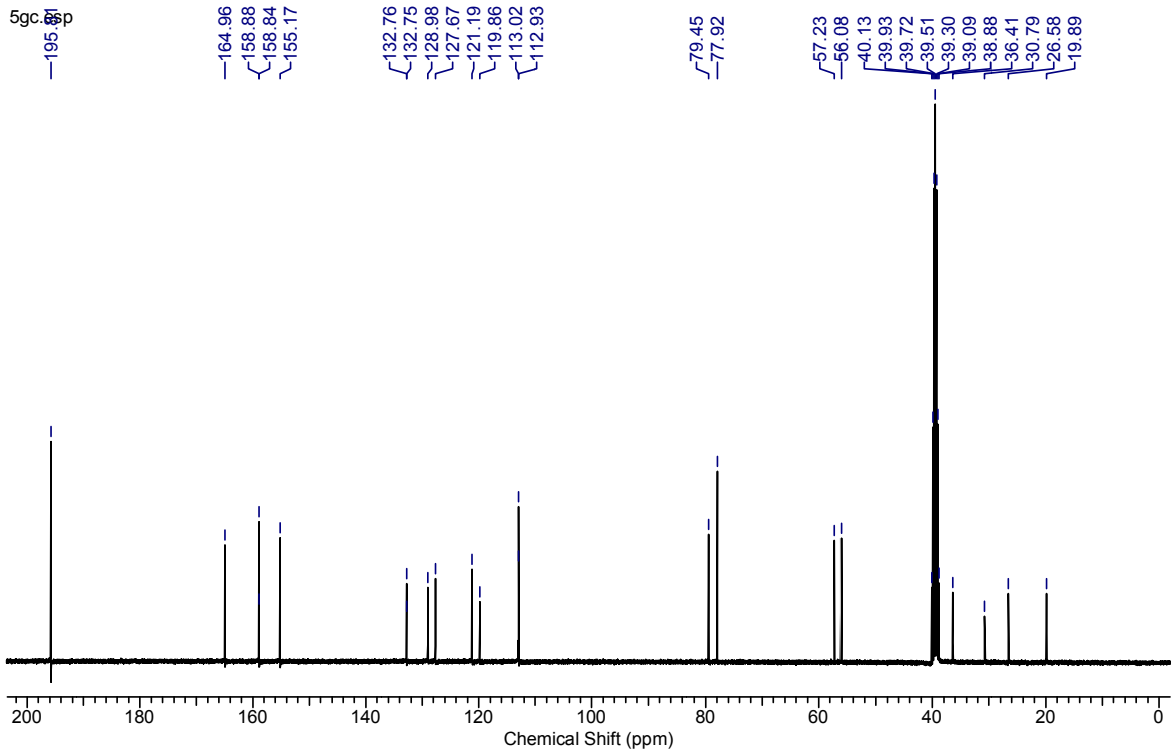


Figure SM 4.2.5.1.5.14. ^{13}C NMR (100 MHz, DMSO-d_6) of Compound ***5g***

Hantzsch synthesis of nifedipine

Supplementary Material

Experiment Notes

Background information

Melting point, IR and MS data

Table of ^{1}H NMR data

Figures

Photos of the experiment

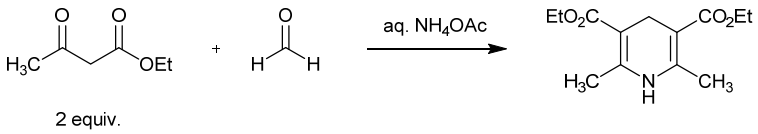
^{1}H and ^{13}C NMR spectra

IR spectrum

Mechanism

HPLC analysis

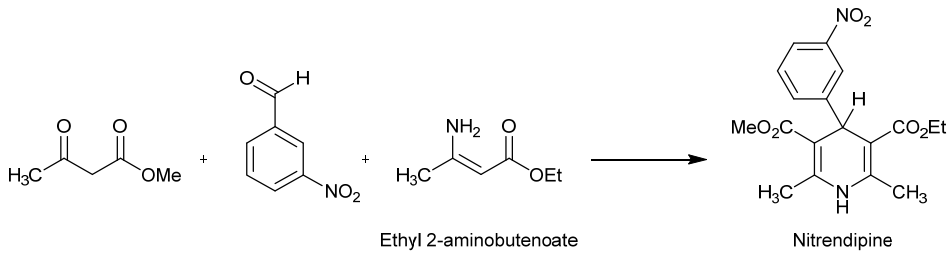
The standard Hantzsch dihydropyridine synthesis experiment used in teaching labs usually employs ethyl acetoacetate, formaldehyde and an ammonium salt (Scheme SM 4.2.5.2.1).[1,2,3] Urotropine is sometimes used in lieu of aqueous formaldehyde.[4]



Scheme SM 4.2.5.2.1 – Commonly used example of a Hantzsch dihydropyridine synthesis.

In this experiment students carry out a Hantzsch synthesis to make nifedipine, an anti-hypertensive drug, in a single step from methyl acetoacetate, ammonia and an aromatic aldehyde (*ortho*-nitrobenzaldehyde). Unlike acetylsalicylic acid and paracetamol which can also be prepared in a single step, nifedipine has a more complex heterocyclic structure and its preparation involves a multi-component reaction. The experiment illustrates the importance of heterocyclic chemistry, particularly to students specialising in pharmaceutical chemistry.

Nifedipine was introduced as an antihypertensive drug in the 1980s. Second-generation drugs of the nifedipine type are no longer symmetrical and they possess different ester groups. Nitrendipine, for example, is made by a variant of the Hantzsch synthesis using equal amounts of an aldehyde, methyl acetoacetate and ethyl 2-aminobutenoate (Scheme SM 4.2.5.2.2). Its synthesis requires no further source of ammonia. Ethyl 2-aminobutenoate is a stable enamine that is readily obtained from the β-ketoester and ammonia.



Scheme SM 4.2.5.2.2 – Preparation of nitrendipine.

The procedure for the Hantzsch synthesis of nifedipine has been adapted from a patent publication.[5] Students have encountered few problems with this experiment over the years, although yields can vary between 25 and 60%, which reflect mostly a student's recrystallisation skills. The limiting reagent is the aldehyde (theoretical yield of nifedipine = 15.0 mmol or 5.19 g).

At Heriot-Watt University Chemistry students have a series of lectures on heterocyclic chemistry during the course of Year 3. They also carry out the synthesis of several heterocycles of which the Hantzsch dihydropyridine synthesis is an example. Only students specialising in pharmaceutical chemistry are asked to make nifedipine since the experiment complements their specialist lecture course.

The scale of the experiment produces a sufficient amount of nifedipine that recrystallisation provides no problems. Students are asked to characterise their samples by IR, HPLC and melting point. Copies of ^{1}H and ^{13}C NMR spectra are generally provided.

M.p.: 169-171 °C (yellow crystalline solid).[6]

Photos of the experiment

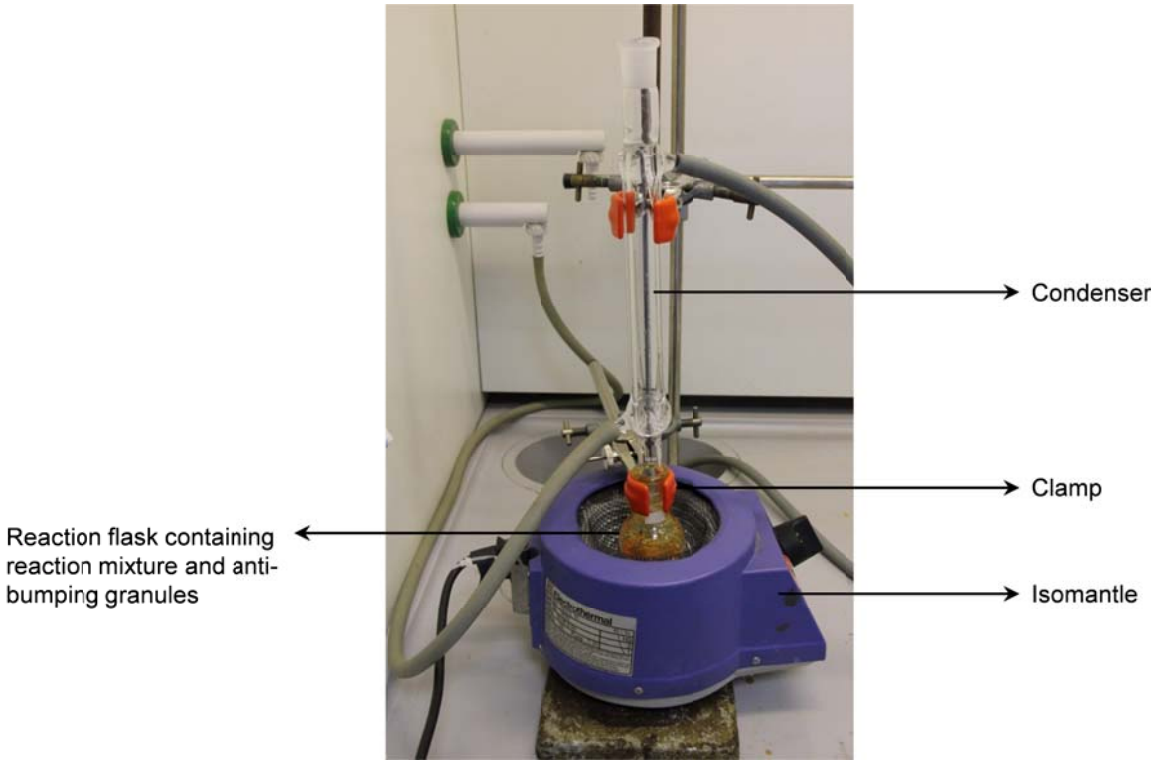


Figure SM 4.2.5.2.1 – Reaction mixture during the reflux step. Formation of nifedipine is evident from the yellow-orange colour of the solution.

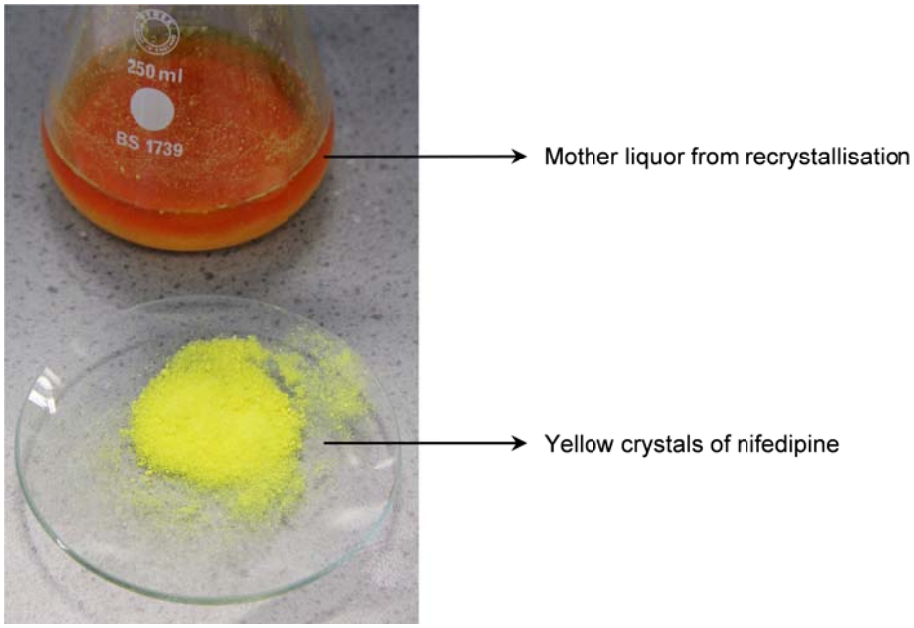


Figure SM 4.2.5.2.2 – Nifedipine after recrystallisation and filtration (student sample).

^{1}H and ^{13}C NMR spectra

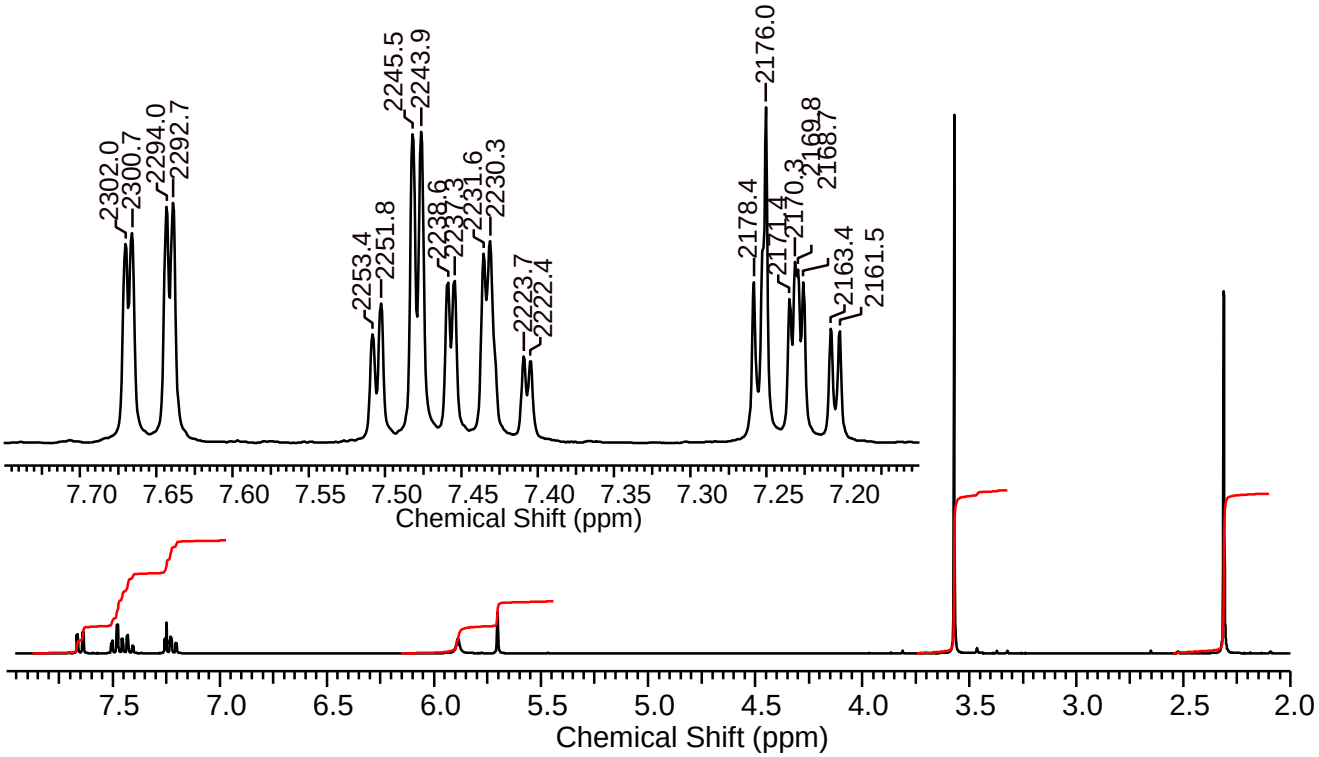


Figure SM 4.2.5.2.3 – ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the recrystallised nifedipine.

Table SM 4.2.5.2.1 – ^{1}H NMR data for nifedipine.

δ_H	Integral	Multiplicity	Inferences
2.31	6H	Singlet	CH_3 next to C
3.57	6H	Singlet	CH_3 next to O
5.70	1H	Singlet	CH of dihydropyridine
5.89	1H	Singlet (broad)	NH
7.23	1H	~Triplet of doublets [a,b]	Aromatic CH (overlaps with $CHCl_3$ singlet)
7.43	1H	Triplet of doublets [a]	Aromatic CH
7.49	1H	Doublet of doublets [a]	Aromatic CH
7.65	1H	Doublet of doublets [a]	Aromatic CH

a) A pair of triplets of doublets and a pair of doublets of doublets are a characteristic feature of an *ortho*-disubstituted benzene. **b)** This signal is best described as a doublet of doublet of doublets, with two slightly differing *ortho* couplings.

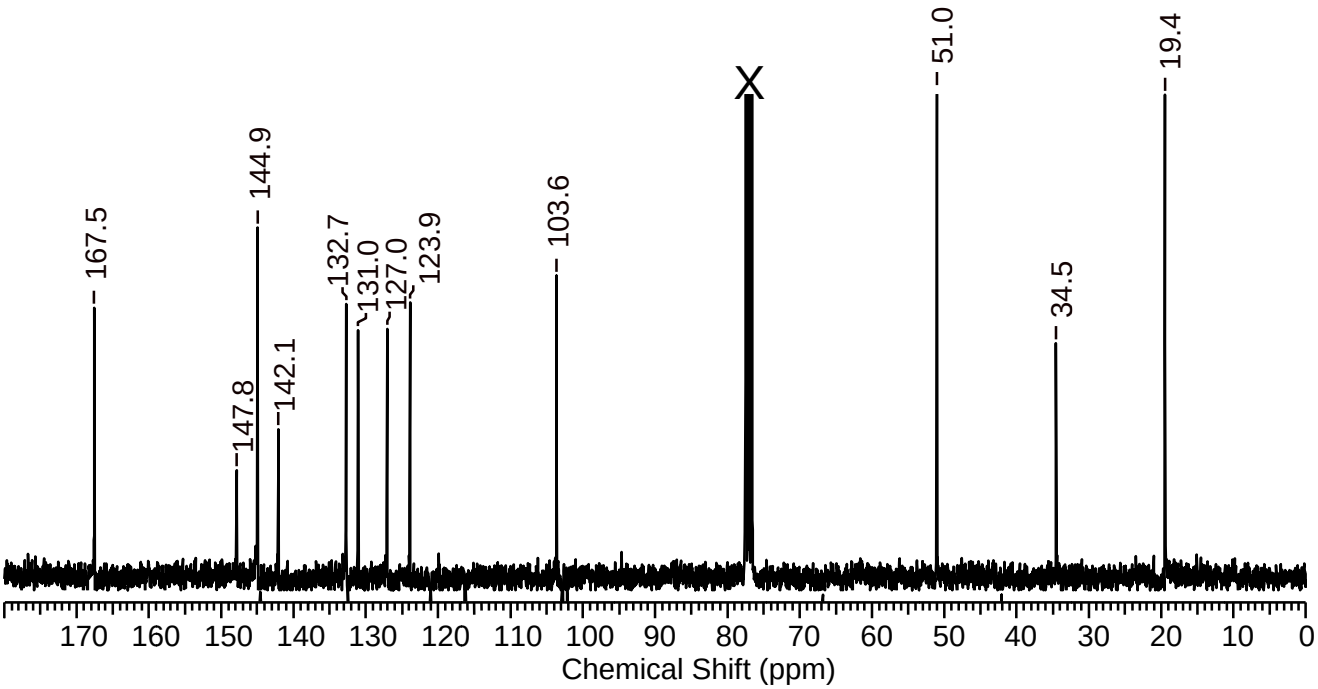


Figure SM 4.2.5.2.4 – ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of the recrystallised nifedipine. Solvent signals are marked by "X".

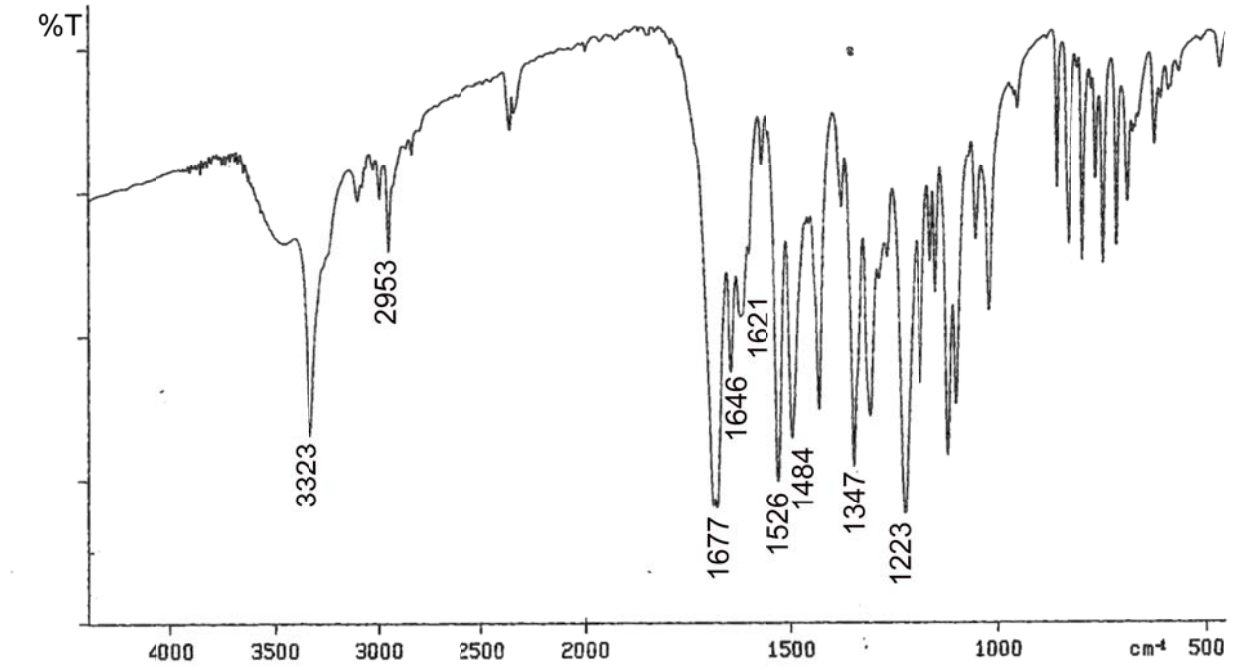


Figure SM 4.2.5.2.5 – ATR-IR spectrum (neat solid, student sample) of the recrystallised nifedipine.

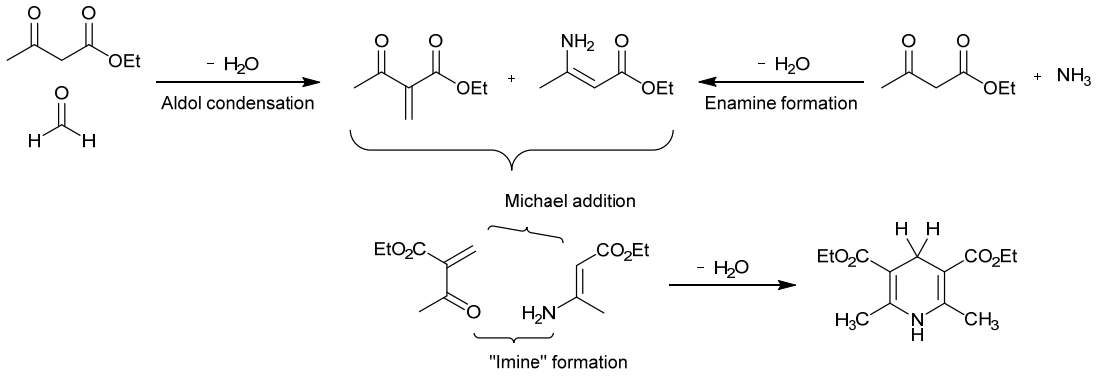
IR (Figure SM 4.2.5.2.5): 3323 cm^{-1} (N-H stretch), 1677 cm^{-1} (C=O stretch), 1646 cm^{-1} (C=C stretch).

MS: *m*/*z* = 346 ($M^{\bullet+}$), 329 ($M^{\bullet+}$ – OH, NB: the oxygen originates from the NO_2 group + the 4-H), 224 ($M^{\bullet+}$ – *o*-$NO_2C_6H_4$).[7]

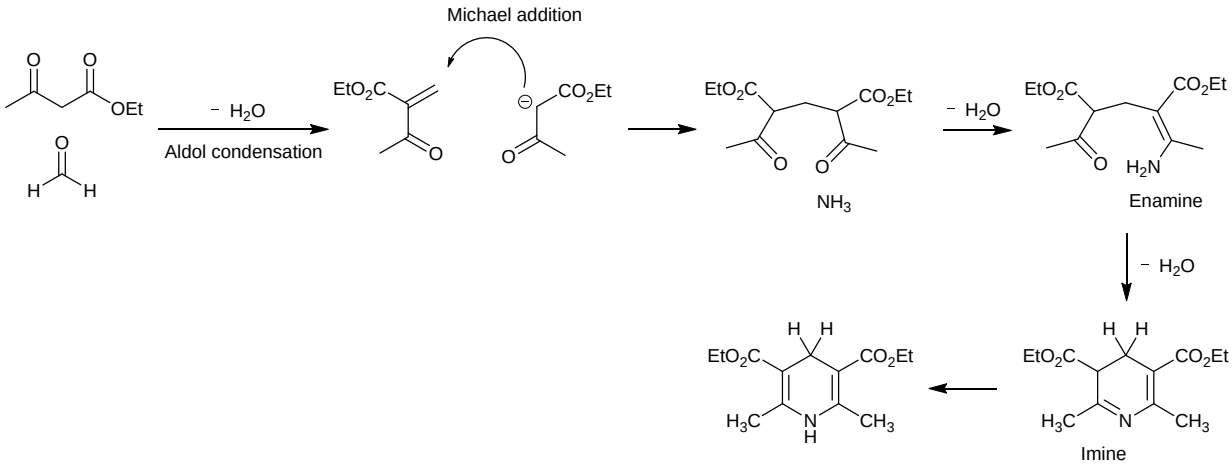
Mechanism

A detailed discussion of the mechanism of this reaction can be found in the literature.[8,9]

The key steps include an aldol condensation, a Michael addition, an enamine formation and a cyclisation. However, various routes are possible, some of which are outlined in Schemes SM 4.2.5.2.3 and SM 4.2.5.2.4.[10]



Scheme SM 4.2.5.2.3 – Outline mechanism for the formation of nifedipine.



Scheme SM 4.2.5.2.4 – Alternative outline mechanism for the formation of nifedipine.

HPLC analysis

Nifedipine is generally obtained in high purity. Student samples on occasion still contain traces of recrystallisation solvent, starting materials or intermediates from the synthesis. Only the latter are UV-active and can be picked up in a HPLC trace.

Typical HPLC conditions: 2 mg of sample dissolved in 2 mL of HPLC-grade methanol; a suitable eluent is 70%/30% methanol/water, pumped at 1.0 mL/min; C18 reversed phase column; detection at 256 nm (Figure SM 4.2.5.2.6).

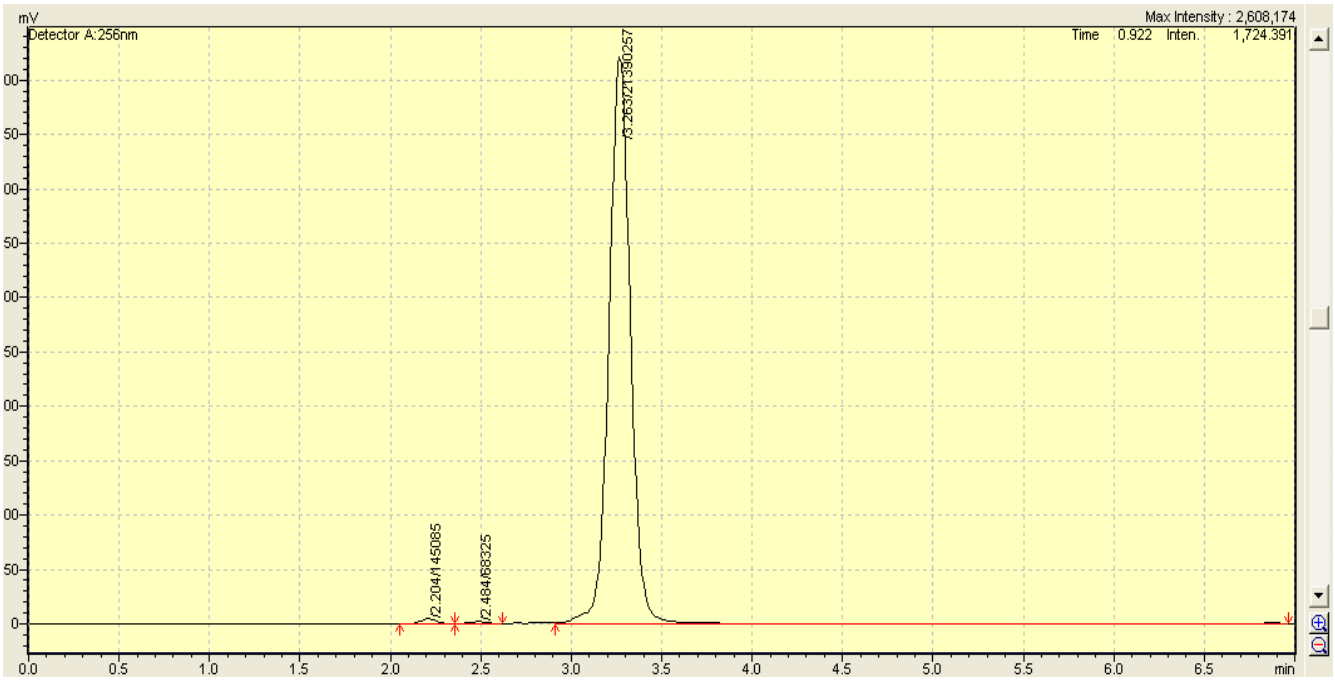


Figure SM 4.2.5.2.6 – Typical HPLC trace of a recrystallised nifedipine sample (student sample).

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[1] L. L. W. Cheung, S. A. Styler and A. P. Dicks, *J. Chem. Educ.*, 2010, **87**, 628-630.
[2] B. E. Norcross, G. Clement and M. Weinstein, *J. Chem. Educ.*, 1969, **46**, 694-695.
[3] Synthesis of 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester, http://www.oc-practikum.de (accessed September 2014).
[4] Chemistry Olympiad of the Baltic States Practical Examination (Riga 2006), ftp://ftp.ttkool.ut.ee/chem/balt/bko0506exp_eng.pdf (accessed September 2014).
[5] F. Bossert and W. Vater (Bayer AG), *US Pat*. 3,485,847 (1969). Accessed through Google Patents, https://www.google.com/?tbm=pts&gws_rd=ssl (accessed August 2014).
[6] In case a student has accidentally used ethyl acetoacetate instead of methyl acetoacetate, this will be evident from the lower m.p. of 118 – 120 °C. If in doubt, a ^{1}H NMR will show an ethyl signal with diastereotopic CH_2 protons. K. L. Bridgwood, G. E. Veitch and S. V. Ley, *Org. Lett*., 2008, **10**, 3627-3629.

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[7] MS data from SDBSWeb, National Institute of Advanced Industrial Science and Technology: http://sdbs.db.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi (accessed August 2014).
[8] U. Eisner and J. Kuthan, *Chem. Rev*. 1972, **72**, 1-42.
[9] K. M. Bucholtz, J. D. Hugdahl, A. M. Kiefer, K. M. Kiefer and A. M. S. Maria, *Chem. Educator*, 2012, **17**, 125-127.
[10] J. A. Joule and K. Mills, *Heterocyclic Chemistry*, 4th ed., Blackwell Publishing, Oxford, 2000, 104-105.

A Ugi multicomponent reaction in the synthesis of *N*-cyclohexyl-2-(*N*-(4-methoxybenzyl)acetamido)-2-(thien-2'-yl)acetamide

Supplementary Material

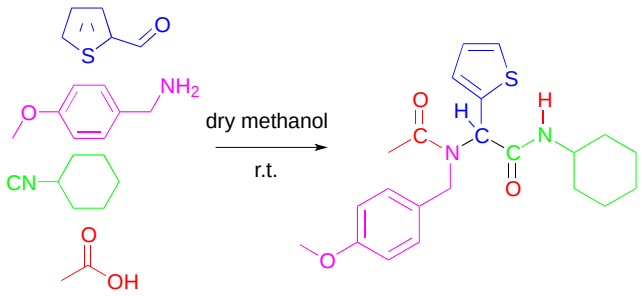
1. Experiment notes

This experiment involves simple experimental techniques and commercially available reagents, and it is expected that the students possess previously acquired practical skills (in terms of isolation and purification techniques) and theoretical background (synthesis, reactivity and spectroscopic data interpretation). Therefore, this experiment may be appropriate for last year project in Chemistry degree or as the practical component of advanced chemistry subjects at Master level.

The synthesis of the title compound is achieved by a four-component condensation reaction, the Ugi reaction, by reacting an amine, a carbonyl compound, an acid and an isocyanide.

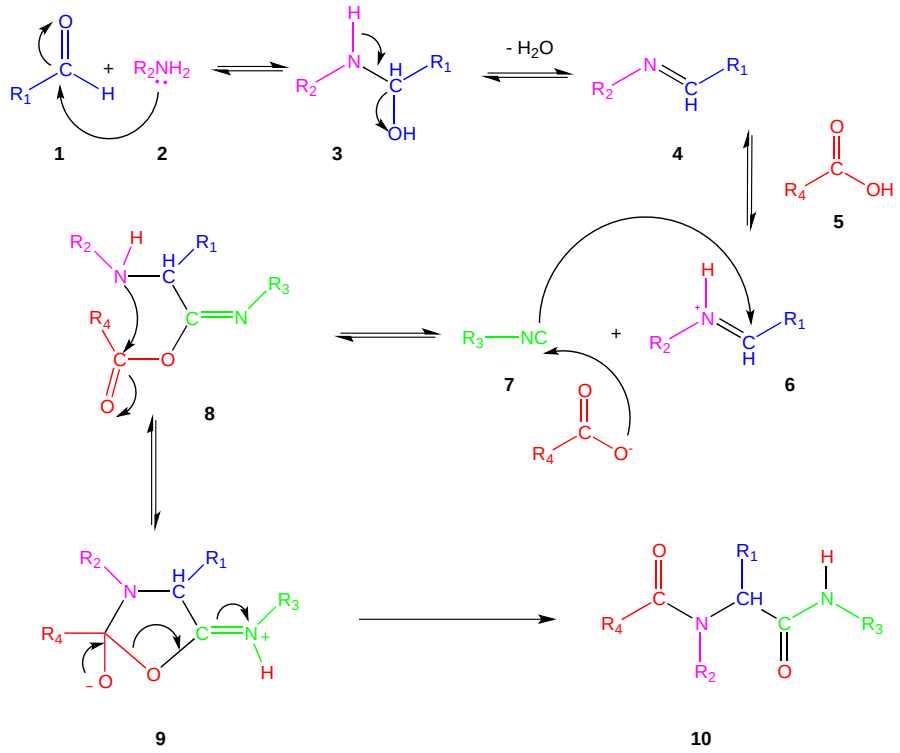
The Ugi reaction is based on a previous three-component reaction proposed earlier by Passerini, which involved the reaction of a carboxylic acid, a carbonyl compound and an isocyanide to yield α-acyloxycarboxamides. Since the carbonyl group of aldehydes and ketones is isoelectronic with the imino group, Ugi decided to add an extra reagent (the amine) thus developing a novel four-component reaction that produces α-acylamidocarboxamides. The final product is obtained by combination of all reagents with the loss of a water molecule.

In the present experiment, thiophene-2-carboxaldehyde, 4-methoxybenzylamine, acetic acid and cyclohexylisocyanide are reacted in order to obtain the corresponding *N*-cyclohexyl-2-(*N*-(4-methoxybenzyl)acetamido)-2-(thien-2'-yl)acetamide (Scheme SM 4.2.5.3.1). In the present experiment conditions, in various repetitions carried out by third year Chemistry students and first year Chemistry MSc students, the product was obtained in 30-40% yield as orange oil.



Scheme SM 4.2.5.3.1. Preparation of *N*-cyclohexyl-2-(*N*-(4-methoxybenzyl)acetamido)-2-(thien-2'-yl)acetamide by a Ugi reaction.

As for the mechanism, the reaction is initiated by nucleophilic substitution of the amine **2** with the aldehyde **1**, via hydroxylamine **3**, yielding the imine **4**. Protonation of the imine nitrogen by carboxylic acid **5** increases the electrophilic character of the C=N bond in the resulting imminium cation **6**. This species undergoes nucleophilic attack by the isocyanide **7**, followed by the nucleophilic attack of the carboxylate anion, resulting in intermediate **8**. Finally a rearrangement occurs through intermediate α-acylaminoamide **9** with an *O*- to *N*-acyl transfer to yield the final product **10** (Scheme SM 4.2.5.3.2). All the steps are in equilibrium except for the last acyl transfer which is irreversible.



Scheme SM 4.2.5.3.2. Mechanism of the Ugi reaction.

Although the condensation of the four reagents can be done at the same time, it is advantageous to form the imine prior to the addition of the other components, to increase the final yield. The Passerini reaction may occur as a side reaction in certain conditions (use of nonpolar solvents, bulky reagents).

This experiment has been replicated with other aldehydes (a series of 5-phenylthiophene-2-carboxaldehyde bearing different substituents of different electronic character at the phenyl ring) and other commercial isocyanides (liquid or solid) and the procedure and results were reproducible. The isocyanide used in this experiment was chosen for being a liquid, which minimizes the risks associated with the handling of this smelly reagent.

2. Figures

2.1. Reaction setup

Figure SM 4.2.5.3.1. Reaction setup for the Ugi reaction.

2.2. Reaction mixture filtration setup

Figure SM 4.2.5.3.2. Reaction mixture filtration setup after the Ugi reaction.

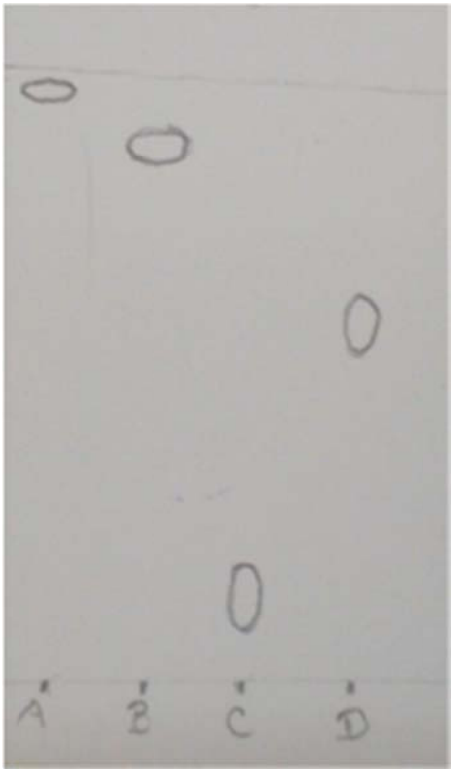
2.3. Rotary evaporation of reaction mixture

Figure SM 4.2.5.3.3. Rotary evaporation of solvent from reaction mixture.

2.4. Column chromatography purification of the evaporated crude residue

Figure SM 4.2.5.3.4. Column chromatography purification of the evaporated crude residue.

2.5. Photo of the TLC plate (to check the course of column chromatography)



A – isocyanide

B – aldehyde

C – amine

D – product

Retention factors, R_f

A – isocyanide	$R_f = 0.96$
B – aldehyde	$R_f = 0.87$
C – amine	$R_f = 0.14$
D – product	$R_f = 0.62$

Figure SM 4.2.5.3.5. Photo of the TLC plate with the reagentes and product (eluent: dichoromethane)

2.6. ^{1}H and ^{13}C NMR spectra of the product

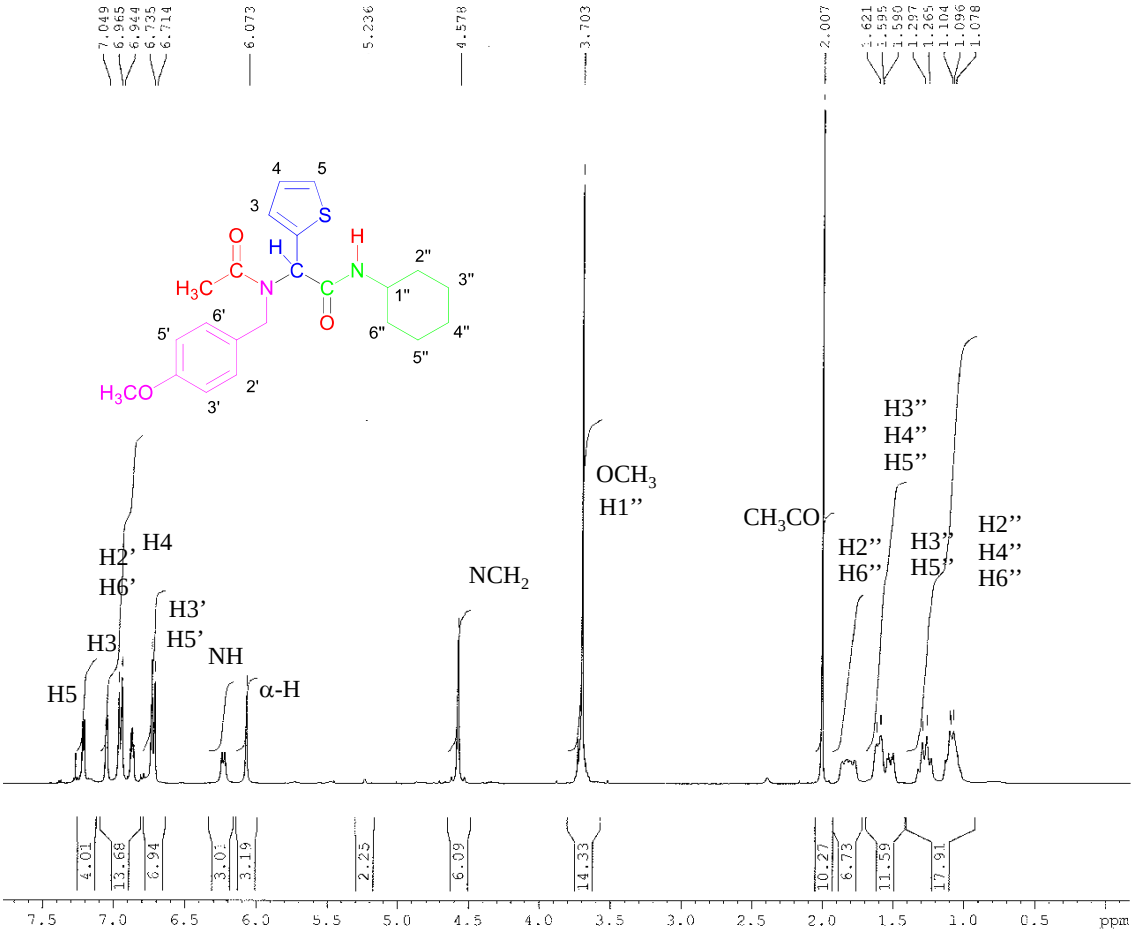


Figure SM 4.2.5.3.6. ^{1}H NMR spectrum of the product in $CDCl_3$ obtained in a Bruker Avance III spectrometer operating at 400 MHz at 25ºC.

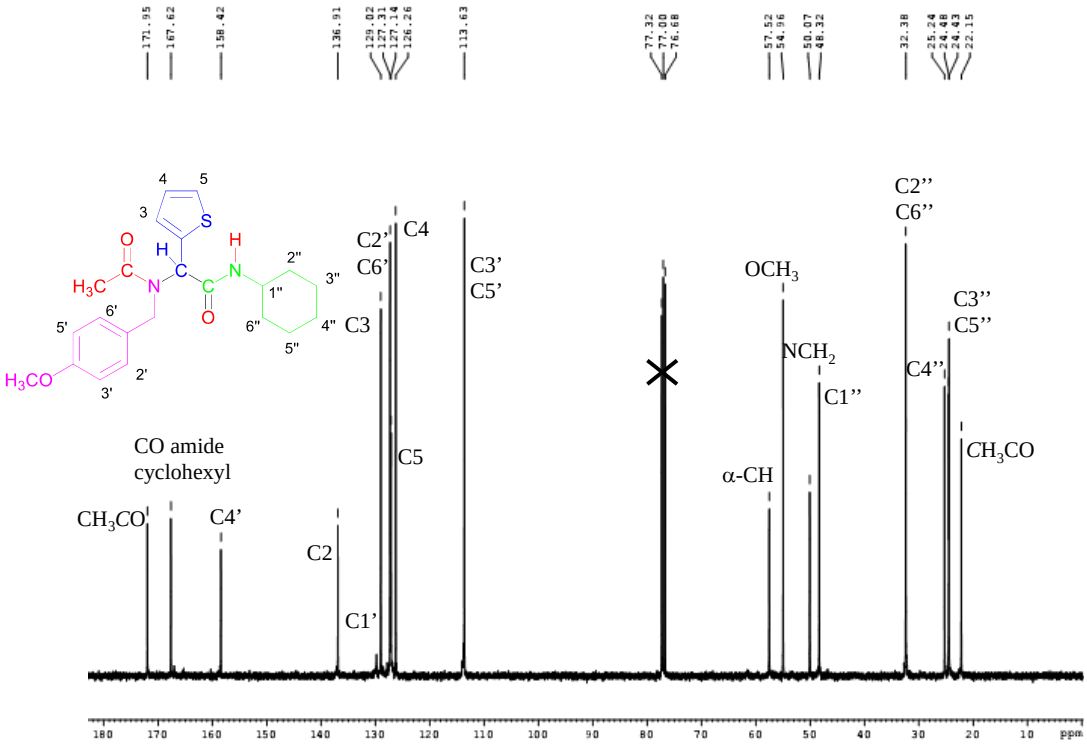


Figure SM 4.2.5.3.7. ^{13}C NMR spectrum of the product in $CDCl_3$ obtained in a Bruker Avance III spectrometer operating at 100 MHz at 25ºC.

Preparation of phenylglycine and hydroxymorpholine derivatives through a Petasis borono-Mannich reaction

Supplementary Material

The main purpose of this experiment is to illustrate the use of multicomponent reactions as a remarkable tool for the easy preparation of a small library of compounds. The experimental simplicity of this kind of reactions in the preparation of moderately complex molecules resultant from the formation of new carbon-carbon bonds in one the aspects that should be highlighted with this experiment. It also aims to draw the students' attention to the commercial availability and diversity of boronic acids and their use in organic synthesis, in the context of a more sustainable chemistry.

Due to the incorporation of almost every atom of the reactants into the product in a multicomponent reaction, this type of reaction is attractive from a sustainable point of view. In this experiment, emphasis can be given to this aspect. Besides boron, all atoms from the starting materials are incorporated in the reaction product. The liberation of boron in the boric acid form ($B(OH)_3$) poses no toxicity problems to the procedure since this can be easily removed from the mixture through a simple filtration or by extracting the aqueous mixture with an organic solvent, if the product is soluble in water. The use of water as the reaction medium allows the easy isolation of the reaction product and avoids the use of organic solvents as reaction solvent or in the purification step.

The student body is advanced organic chemistry students, in which the concepts of amine formation and Mannich reactions were taught. The students should be skilled enough in order to perform the reaction at a micro-scale as here planned.

Both experiments were designed in order to be performed at a micro-scale (so that the students would get around 50 mg of each product), which implies the use of unusual glassware and some unusual techniques in teaching laboratories. The execution of these experiments at a larger scale might need increased reaction times due to the heterogeneous nature of the reaction mixture.

Additional notes on the preparation of *N,N*-dibenzyl phenylglycine: This procedure was successfully implemented at the described scale, and product yields around 80 % were obtained when performed by experienced researchers and 54 % average yield (50-58 % range) when executed by four upper-division undergraduate students.

Regarding the tricky steps of this work, some special concern is needed for the filtration step. The instructor should check that the cotton is tight in the Pasteur pipette and aware the students for them to avoid the compound drag in the cotton (**Figure SM 4.2.5.4.1**).

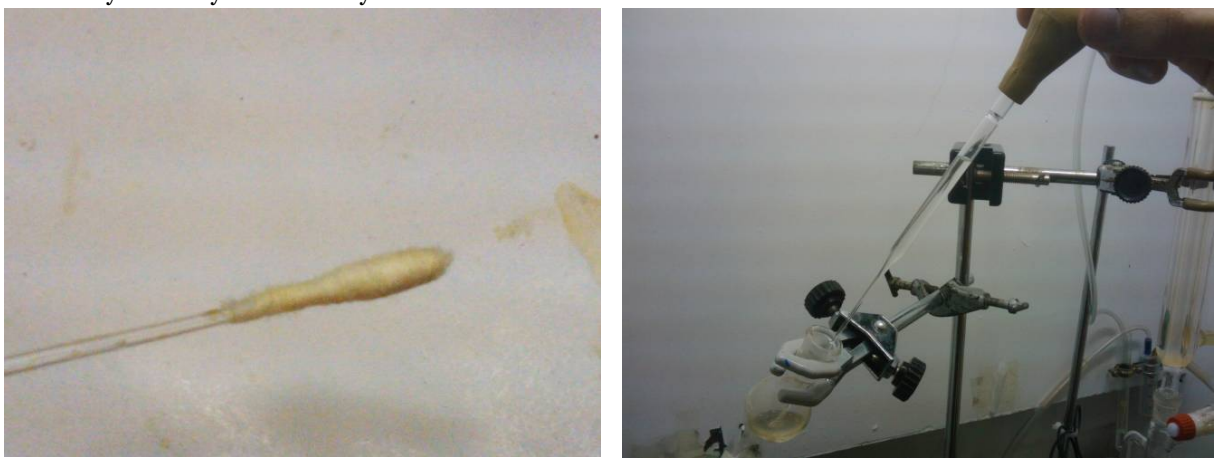


Figure SM 4.2.5.4.1 - Filtration over cotton aided by Pasteur Pipette

Due to the difficulty in properly drying the product in a vacuum pump in a short time, it is suggested for the students to re-dissolve the compound in dichloromethane and use a drying agent such as sodium sulphate right after the filtration with the Pasteur pipette.

The ^{1}H NMR spectrum should be performed in DMSO-d_6 (**Figure SM 4.2.5.4.2)**, once the product is not soluble enough in $CDCl_3$ and only spectra of poor quality will be obtained in this solvent.

The melting point of *N,N*-dibenzyl phenylglycine was previously reported in the literature[1]

Additional notes on the preparation of 4-benzyl-3-phenylmorpholin-2-ol: Other experimental conditions were tested. The reaction can be performed at room temperature, needing 24 h to reach completion. At 50 ºC the starting materials were consumed after 5 h. In the latter case, students could obtain the product in 55 % yield in a *cis:trans* 0.2:1 diastereoisomeric ratio and 126-127 ºC melting point. The melting point found in the literature is 148-150 ºC[2], although no data about the diastereoisomeric ratio is given. This aspect can be used for discussion with the students, based on the different diastereomeric composition of the mixture or the existence of polymorphism.

The monitoring of the reaction progress by TLC is difficult due to the proximal R_f values of the product and the boronic acid used, as observed for a silica TLC eluted with Hexane/EtOAc 7:3 after sample dilution with CH_2Cl_2.

The diastereoselectivity of the transformation should be determined based on the ^{1}H NMR spectrum analysis (**Figure SM 4.2.5.4.3)**, namely doublet integration at 4.61 ppm (*trans* diastereoisomer, doublet, J = 7.2 Hz) and 4.87 ppm (*cis* diastereoisomer, doublet, J = 1.7 Hz). The use of large amounts of sample in the NMR tube difficult the proper observation of the peaks multiplicity, particularly for the *cis* diastereoisomer. The NMR spectra of this compound was previously reported in two different publications with different coupling constants[2,3], although with similar chemical shifts.

Due to the complexity of the NMR spectrum of the product, the students should check the 2-(benzylamino)ethanol spectrum available, in order to ensure that no starting material is present.[4]

Other aldehydes: Glycoaldehyde and salicylaldehyde are some examples of other commercially available aldehydes that can be used in the Petasis borono-Mannich reaction.

NMR spectra:

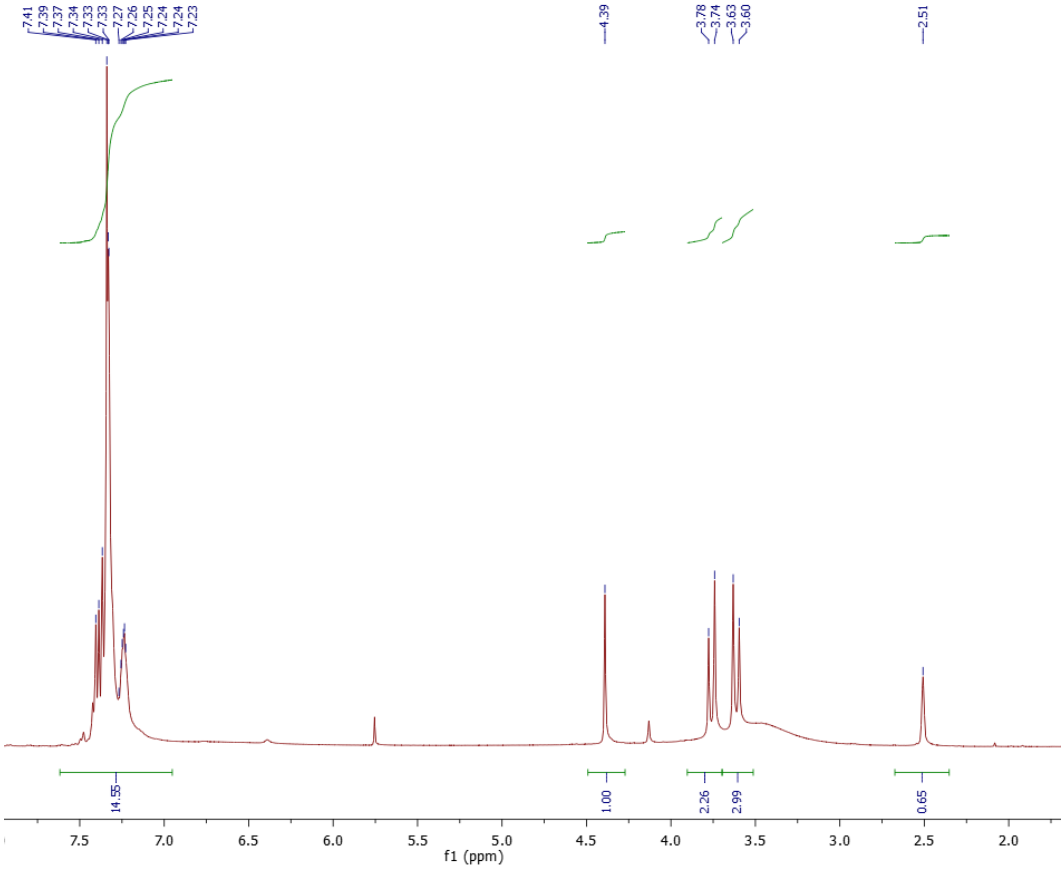


Figure SM 4.2.5.4.2 - ^{1}H NMR of *N,N*-dibenzyl phenylglycine (400 MHz, DMSO)

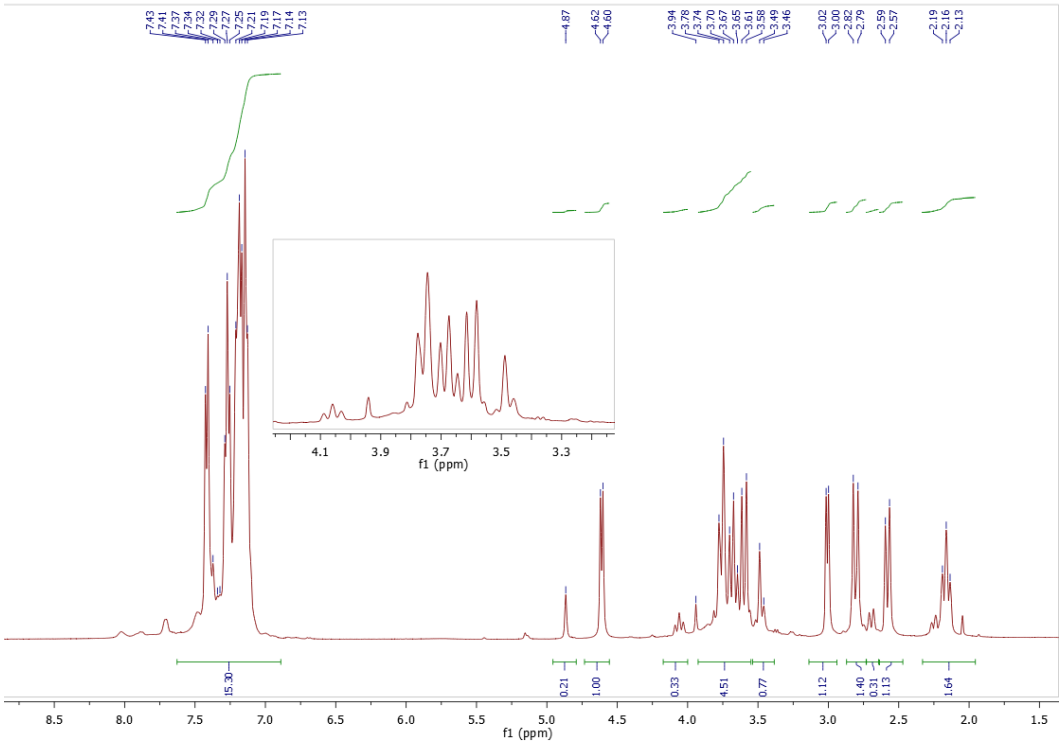


Figure SM 4.2.5.4.3 - ^{1}H NMR of *cis*:*trans* (0.2:1) mixture of 4-benzyl-3-phenylmorpholin-2-ol (400 MHz, $CDCl_3$)

Acknowledgement

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[1] Check compound **7d** in: Camps, P.; Pérez, F.; Soldevilla, N.; Borrego, M. A. *Tetrahedron: Asymmetry* **1999**, *10*, 493.
[2] Compound **8d** in: Berrée, F.; Debache, A.; Marsac, Y.; Collet, B.; Girard-Le Bleiz, P.; Carboni, B. *Tetrahedron* **2006**, *62*, 4027.
[3] Compound **6** in supplementary material of: Hale, J. J.; Mills, S. G.; MacCoss, M.; Shah, S. K.; Qi, H.; Mathre, D. J.; Cascieri, M. A.; Sadowski, S.; Strader, C. D.; MacIntyre, D. E.; Metzger, J. M. *J. Med. Chem.* **1996**, *39*, 1760.
[4] SDBSWeb : http://sdbs.riodb.aist.go.jp (National Institute of Advanced Industrial Science and Technology, April 2014) – SDBS No 12547.

A multicomponent reaction of isocyanides for the synthesis of 4-chromanone-2-carboxamides

Supplementary Material

Notes for the instructor

The experiment was performed as part of the teaching laboratory sessions corresponding to a course of Bioorganic Chemistry included in the fourth year of the BSc in Biochemistry. Protocol A was comfortably performed with groups of 8-10 students organized in teams of 2. However, as microwave irradiation times are very short, it can be easily adapted to larger groups, even if only one microwave reactor is available. The experiment can be also performed at room temperature, with no need of microwave activation (protocol B), although this procedure was only carried out by the authors, and not tested with students. In this later case, both reactions should be set up in the first lab session and left overnight. Work up and analysis should then be performed in the next day lab session. An additional advantage of protocol B is that the reaction with water at room temperature only requires an equimolar amount of isocyanide. Conversely, an excess of isocyanide must be used in the same reaction under microwave activation (protocol A), as significant isocyanide hydrolysis is produced in these conditions.

Both reactions give reasonably pure products with either of the two protocols. However, sometimes a small amount of isocyanide is left unreacted, especially when the reactions are performed at room temperature (Protocol B). Addition of a small amount of 10% aqueous HCl effectively hydrolyses any excess of isocyanide (Figure 1). The reaction with water usually develops a red colour that is also removed by the addition of HCl. If highly pure products are required, the reaction crude can be optionally purified by flash column chromatography on SiO_2, eluting with a gradient of hexane–EtOAc.

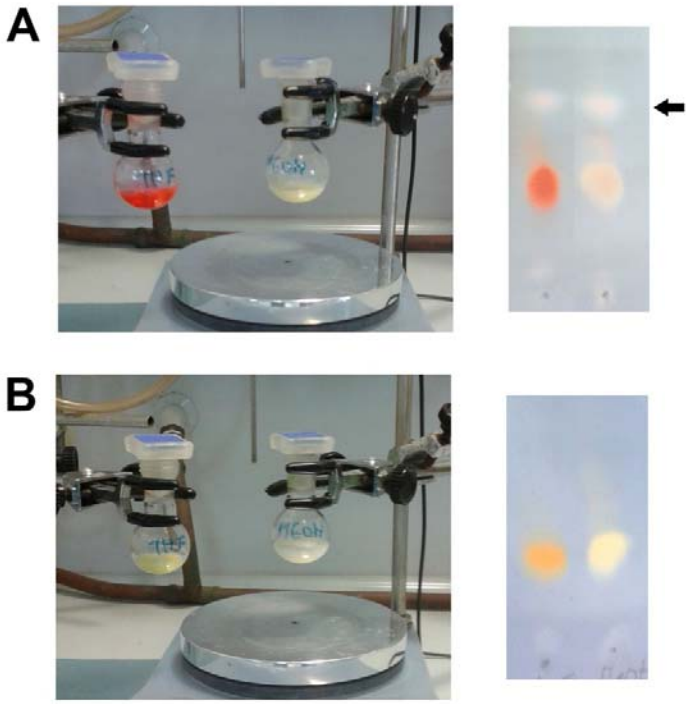


Figure SM 4.2.5.5.1. Reactions at room temperature before (**A**) and after (**B**) work up with 10% HCl. The flask on the left contains the reaction mixture with water in THF; the flask on the right contains the reaction in methanol. Tlc analysis (SiO_2; hexane-EtOAc, 7:3; developed with 2.5% *p*-anisaldehyde, 1% acetic acid and 3.4% H_2SO_4 in 95% ethanol) of the reaction mixtures shows the disappearance of the spot corresponding to cyclohexyl isocyanide (marked with an arrow) after the addition of HCl. NOTE: Although these reactions do not generate hazardous pressures, for safety reasons we do not recommend the use of closed reaction systems in the classroom.

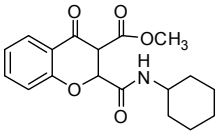
The reaction with water gives an amido carboxylic acid, which spontaneously decarboxylates to afford a chromene 2-carboxamide containing one stereogenic centre. Thus, a single product *N*-cyclohexyl-3,4-dihydro-4-oxo-2*H*-chromene-2-carboxamide as a racemic mixture.

The reaction with methanol gives a mixture of two diastereomeric methyl 2-(cyclohexylcarbamoyl)-4-oxochromane-3-carboxylates which are in equilibrium with the enol tautomer methyl 2-(cyclohexylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate. The NMR analysis of the reaction product shows a mixture of the three isomers in variable proportions, and often only the enol and *cis* isomers are produced. After 24 h in $CDCl_3$ solution, a thermodynamic equilibrium is reached, consisting in a 35:45:25 enol-*trans*-*cis* mixture. This proportion does not change after longer times in solution.

Student's typical yields (Protocol A) range from 70-90% (average 80%) for the reaction with water, and 30-60% (average 45%) for the reaction with methanol.

Liquid reagents were measured using micropipettes with disposable tips.

Spectroscopic data and spectra



Methyl 2-(cyclohexylcarbamoyl)-4-hydroxy-2*H*-chromene-3-carboxylate and **Methyl 2-(cyclohexylcarbamoyl)-3,4-dihydro-4-oxo-2*H*-chromene-3-carboxylate.**

White solid; mp: 119-121 ºC.

IR (cm^{-1}) 3286, 2927, 2853, 1739, 1701, 1655, 1629, 1561, 1440, 1099, 760.

^{1}H NMR (400 MHz, $CDCl_3$) δ **enol**: 12.13 (bs, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.09 (d, *J* = 7.3 Hz, 1H), 5.60 (s, 1H), 3.88 (s, 3H), 3.73-3.61 (m, 1H), 2.10-0.91 (m, 10H); ***cis***: 7.97 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.13 (dd, *J* = 14.3, 8.0 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 1H), 4.95 (d, *J* = 3.2 Hz, 1H), 4.23 (d, *J* = 3.2 Hz, 1H), 3.68 (s, 3H), 3.73-3.61 (m, 1H), 2.10-0.91 (m, 10H); ***trans***: 7.97 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.13 (dd, *J* = 14.3, 8.0 Hz, 2H), 6.38 (d, *J* = 8.0 Hz, 1H), 5.32 (d, *J* = 10.0 Hz, 1H), 4.05 (d, *J* = 10.0 Hz, 1H), 3.85 (s, 3H), 3.73-3.61 (m, 1H), 2.10-0.91 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.62 (C), 170.52 (C), 168.64 (C), 165.78 (C), 165.69 (C), 161.87 (C), 159.25 (C), 155.29 (C), 136. 81 (CH), 136.68 (CH), 133.35 (CH), 128.10 (CH), 127.85 (C), 125.27 (CH), 122.91 (CH), 122.87 (CH), 122.35 (CH), 120.11 (C), 117.83 (CH), 117.76 (C), 117.66 (CH), 116.06 (CH), 92.52 (C), 77.65 (CH), 77.12 (CH), 72.46 (CH), 54.87 (CH), 53.68 (CH_3), 52.90 (CH), 52.82 (CH_3), 52.01 (CH_3), 48.40 (CH), 47.98 (CH), 32.97 (CH_2), 32.91 (CH_2), 32.83 (CH_2), 32.75 (CH_2), 25.48 (CH_2), 25.39 (CH_2), 24.96 (CH_2), 24.85 (CH_2), 24.71 (CH_2), 24.65 (CH_2), 24.47 (CH_2), 24.31 (CH_2).

MS (EI) *m/z* (%) 331 (M^+, 3), 272 (7), 218 (41), 206 (99), 146 (100).

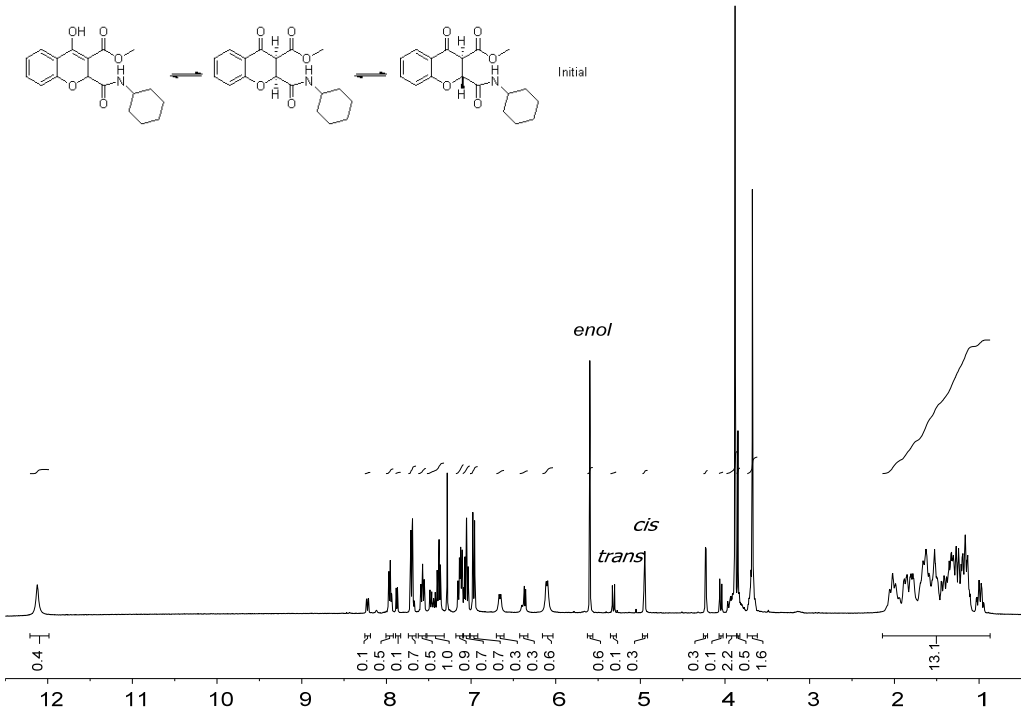


Figure SM 4.2.5.5.2. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of a recently prepared sample of the product of the reaction of chromone-3-carboxylic acid, cyclohexyl isocyanide and methanol.

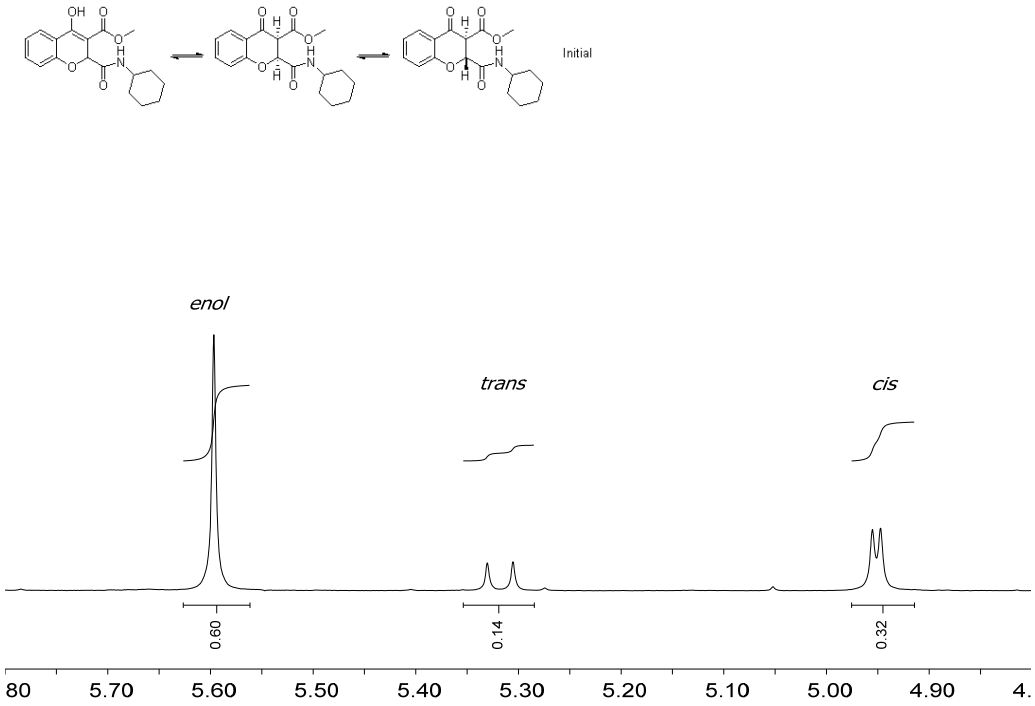


Figure SM 4.2.5.5.3. Expansion of the ^{1}H NMR spectrum of Figure 2, showing the signals corresponding to the proton α to the amide of the three isomers obtained (kinetic mixture).

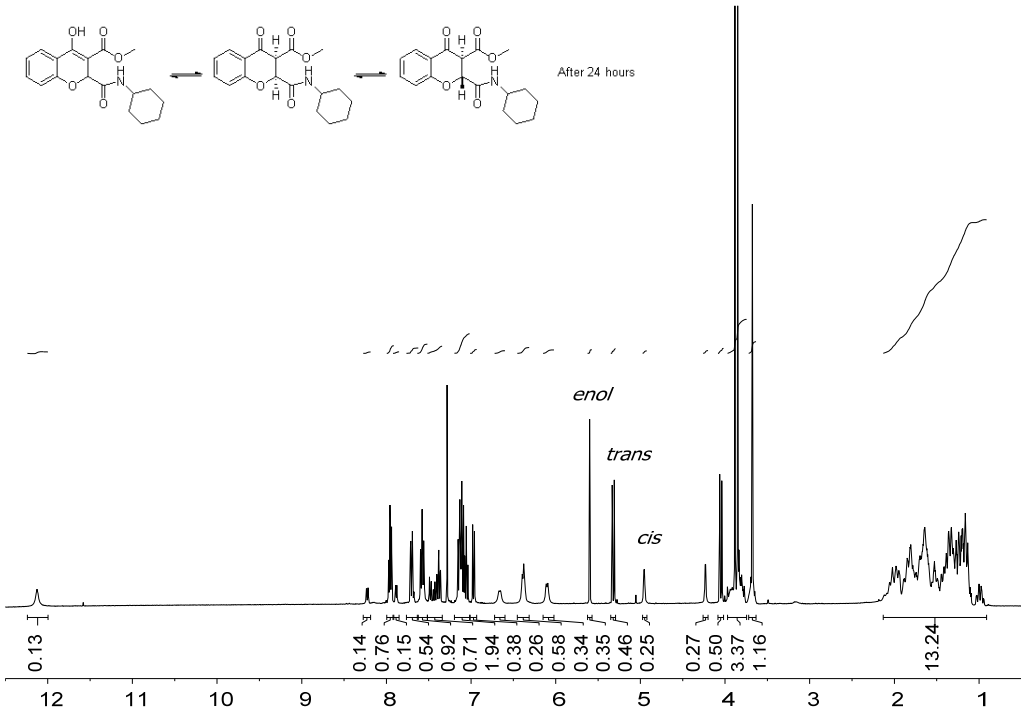


Figure SM 4.2.5.5.4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the product of the reaction of chromone-3-carboxylic acid, cyclohexyl isocyanide and methanol after 24 h in solution.

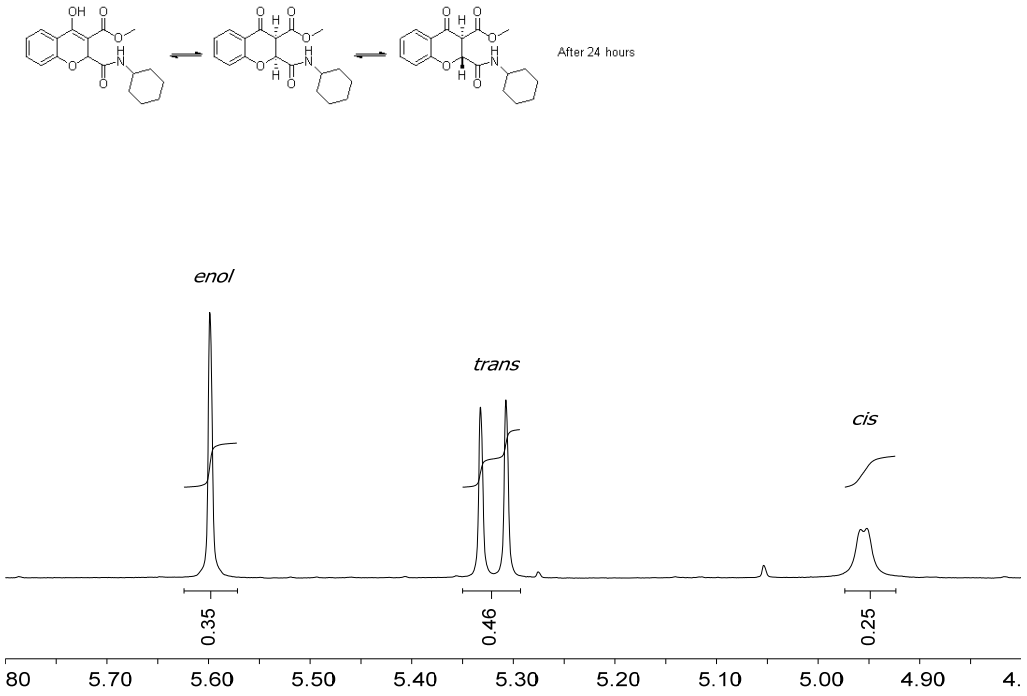


Figure SM 4.2.5.5.5. Expansion of the ^{1}H NMR spectrum of Figure 4, showing the signals corresponding to the proton α to the amide of the three isomers obtained (thermodynamic mixture).

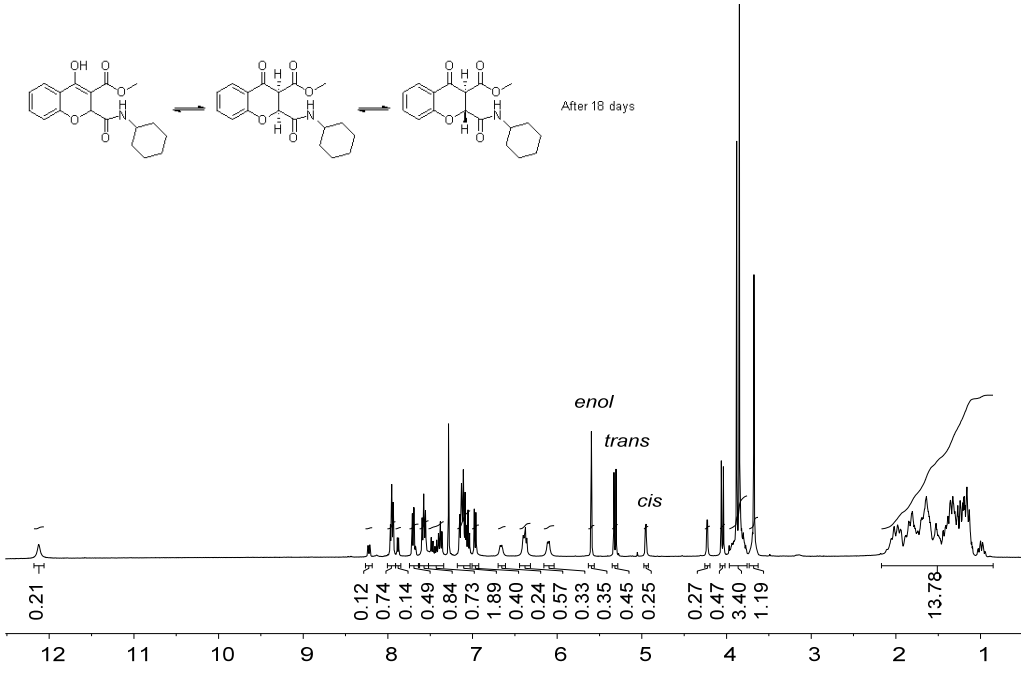


Figure SM 4.2.5.5.6. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the product of the reaction of chromone-3-carboxylic acid, cyclohexyl isocyanide and methanol after 18 days in solution.

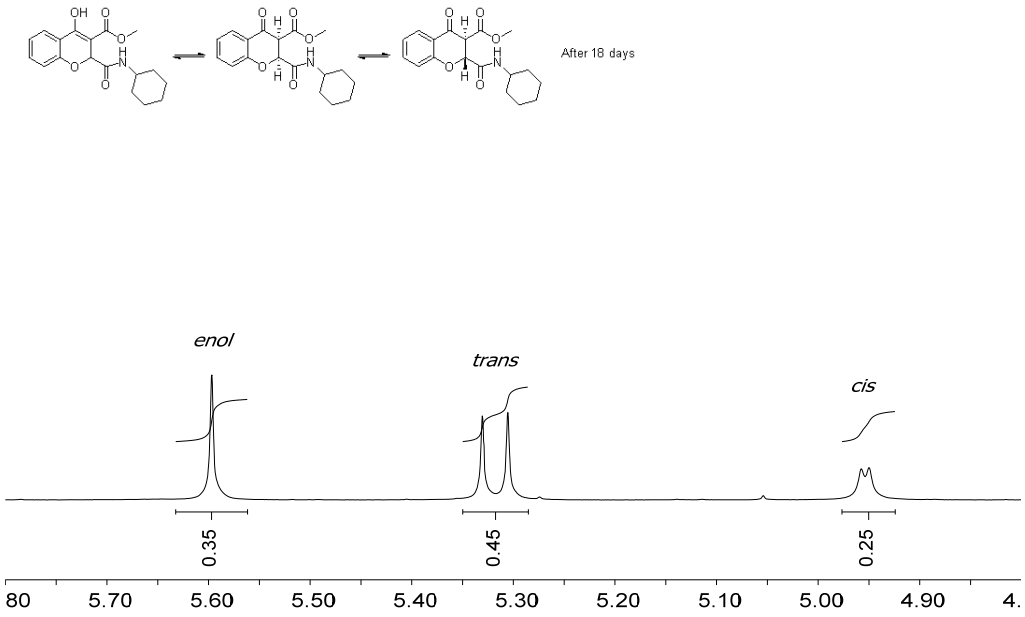


Figure SM 4.2.5.5.7. Expansion of the ^{1}H NMR spectrum of Figure 6, showing the signals corresponding to the proton α to the amide of the three isomers obtained (thermodynamic mixture).

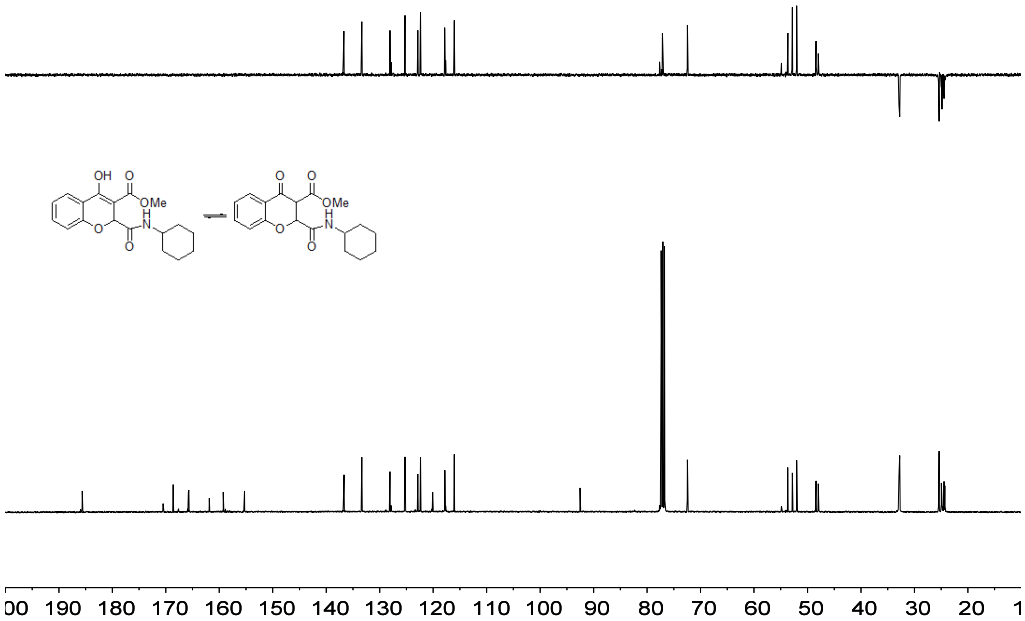
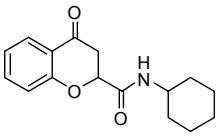


Figure SM 4.2.5.5.8. ^{13}C NMR DEPT spectrum (above) and ^{13}C NMR spectrum (below) (126 MHz, $CDCl_3$) of the product of the reaction of chromone-3-carboxylic acid, cyclohexyl isocyanide and methanol (thermodynamic mixture).



_N_-Cyclohexyl-3,4-dihydro-4-oxo-2_H_-chromene-2-carboxamide

White solid; mp: 144-146 ºC.

IR (cm^{-1}) 3272, 3072, 2928, 2851, 1696, 1655, 1606, 1563, 1463, 1304, 1228, 1118, 764.

^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.55 (dd, *J* = 12.2, 5.0 Hz, 1H), 7.11 (dd, *J* = 15.1, 7.8 Hz, 2H), 6.50 (s, 1H), 4.91 (dd, *J* = 12.9, 3.4 Hz, 1H), 3.96 – 3.82 (m, 1H), 3.21 (dd, *J* = 17.2, 3.4 Hz, 1H), 2.90 (dd, *J* = 17.2, 13.0 Hz, 1H), 2.10 – 1.05 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.30 (C), 167.22 (C), 159.46 (C), 136.25 (CH), 127.36 (CH), 122.55 (CH), 121.25 (C), 117.70 (CH), 76.64 (CH), 48.16 (CH), 40.16 (CH_2), 32.97 (CH_2), 25.43 (CH_2), 24.78 (CH_2).

MS (EI) *m/z* (%) 273 (M^+, 18), 192 (22), 147 (100)

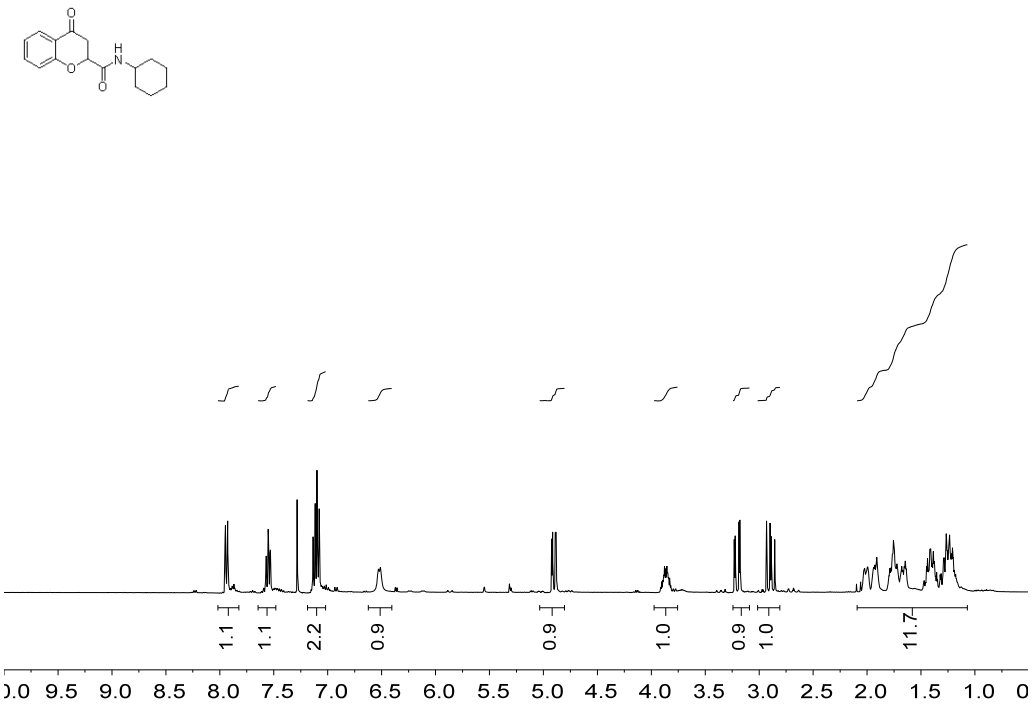


Figure SM 4.2.5.5.9. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the product of the reaction of chromone-3-carboxylic acid, cyclohexyl isocyanide and water.

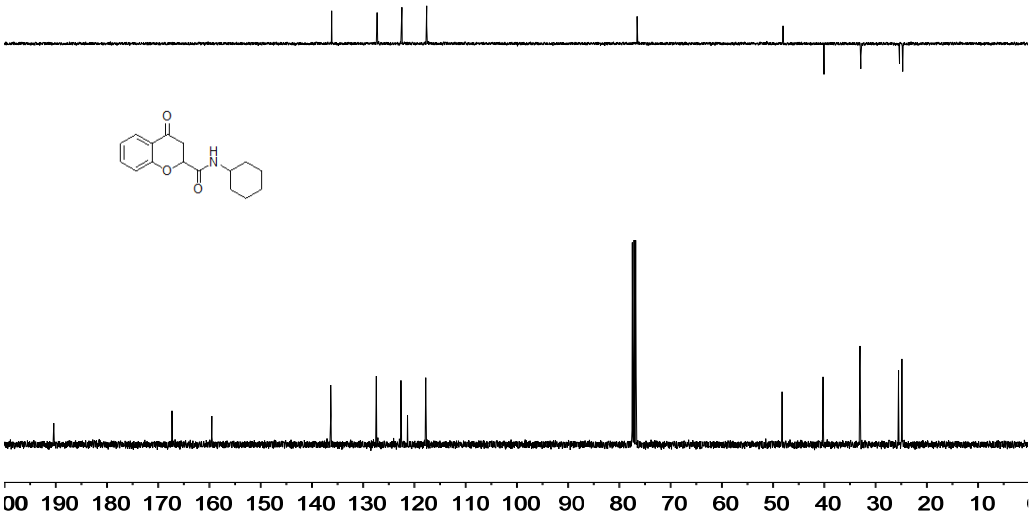


Figure SM 4.2.5.5.10. ^{13}C NMR DEPT spectrum (above) and ^{13}C NMR spectrum (below) (126 MHz, $CDCl_3$) of the product of the reaction of chromone-3-carboxylic acid, cyclohexyl isocyanide and water.