Synthesis of dulcin

Supplementary Material

The synthesis of familiar compounds like analgesics and sweeteners increases the interest of all students for this experiment. Experimental procedure can be easily performed by them, either on a micro or macro scale. Actually this experiment can be run on a single paracetamol® tablet[1]. For the first-year undergraduate students, the reaction sequence usually stops at phenacetin. The second-year undergraduate students can perform the entire multistep synthesis. This experiment proposal provides numerous learning opportunities for introductory organic chemistry students. The amino protection is accomplished by conversion to the less nucleophilic amide[2]. In the Williamson synthesis acid base reactions can be discussed once phenols are more acidic than alcohols so, *p*-hydroxyacetanilide reacts easily with sodium hydroxide to produce the corresponding sodium phenoxide, a conjugate base in which the negative charge is stabilized by the aromatic ring[3]. Amide hydrolysis[4] and nucleophilic addition of an aryl amine with an isocyanate[5] generated in situ by an acid-catalyzed elimination of ammonia from urea are also studied.

Additional notes on *p*-hydroxyacetanilide

Reflux setup to obtain *p*-hydroxyacetanilide is shown in **Figure SM 8.1.1**. It is obtained 65-75% yield and melting point 167-170 ºC (169-170.5 ºC)[6].

Figure SM 8.1.1 – Reflux setup.

Additional notes on phenacetin

Initially, phenacetin was prepared according other method involving metallic sodium, absolute ethanol and long reflux period time.[7] The present procedure presents numerous advantages as described previously. **Figure SM 8.1.2** shows the setup for ethyl iodide addition to the reaction mixture.

Figure SM 8.1.2 – Setup after removal of heating bath and addition of ethyl iodide.

Phenacetin is obtained in 75-80% yield by both methods and melting point 125-133 ºC (137.8 ºC) [8] with heating steps of the equipment lower than 2 ºC.

Additional notes on dulcin

Special attention should be given to pH adjustment in this phase. The presence of a precipitate shows that the reaction is complete. The obtained dulcin is quite pure and should be recrystallized from a minimal amount of hot water. In addition, products can be identified by GC analysis and TLC.[9] Dulcin is obtained around 50% yield and overall yield for the three-step conversion of p-aminophenol to dulcin is 30-40%. Melting points recorded by students are lower than expected due to deficient dryness of the product (173-174 ºC).[10]

Figure SM 8.1.3 – Dulcin recrystallization from water. Heating plate and copper funnel (previously heated by flame) for hot filtration

IR spectra:

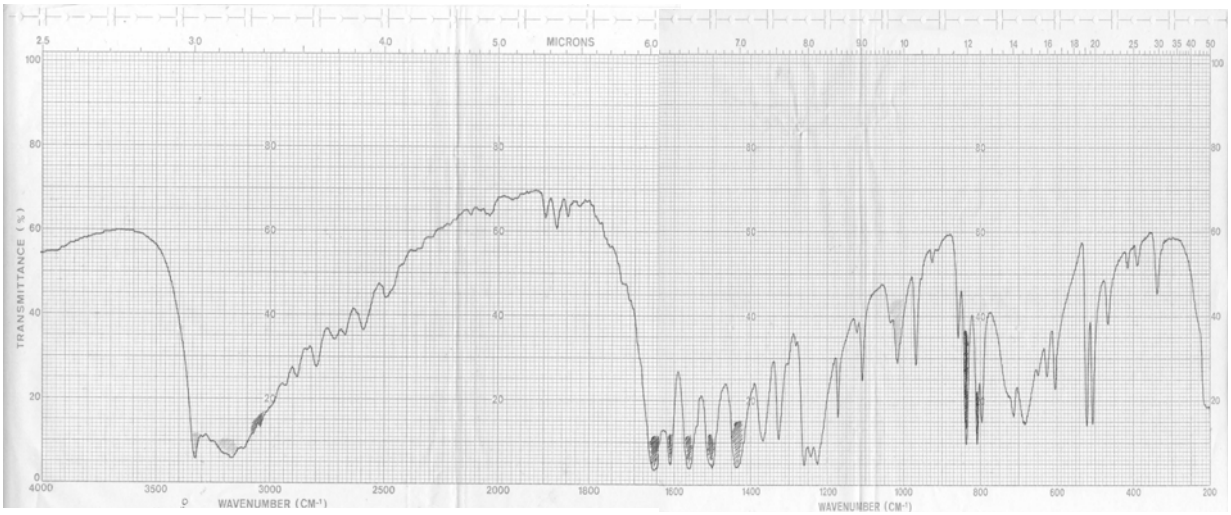


Figure SM 8.1.4 - IR (KBr) of *p*-hydroxyacetanilide

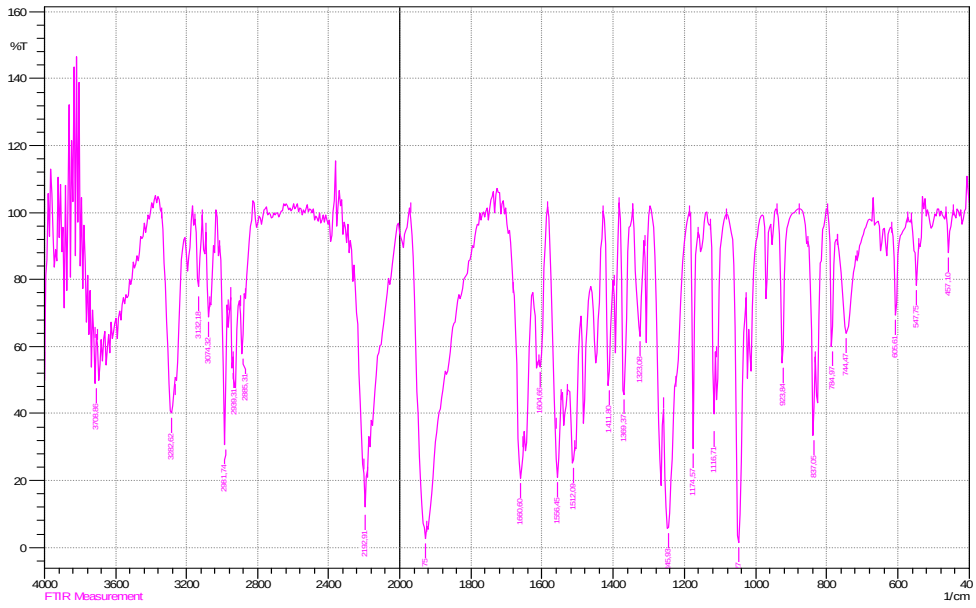


Figure SM 8.1.5 - IR (KBr) of phenacetin

IR spectra of all products are available in the literature (Spectral Database for Organic Compounds, SDBS nº 3290, nº 1413, nº 31799)[11]

NMR spectra:

NMR spectra were obtained with student's samples and present some impurities; nevertheless students easily identify the aromatic protons, CH_2 and CH_3 groups. NH proton absorptions are sensitive to solvent changes causing variations in the shift.

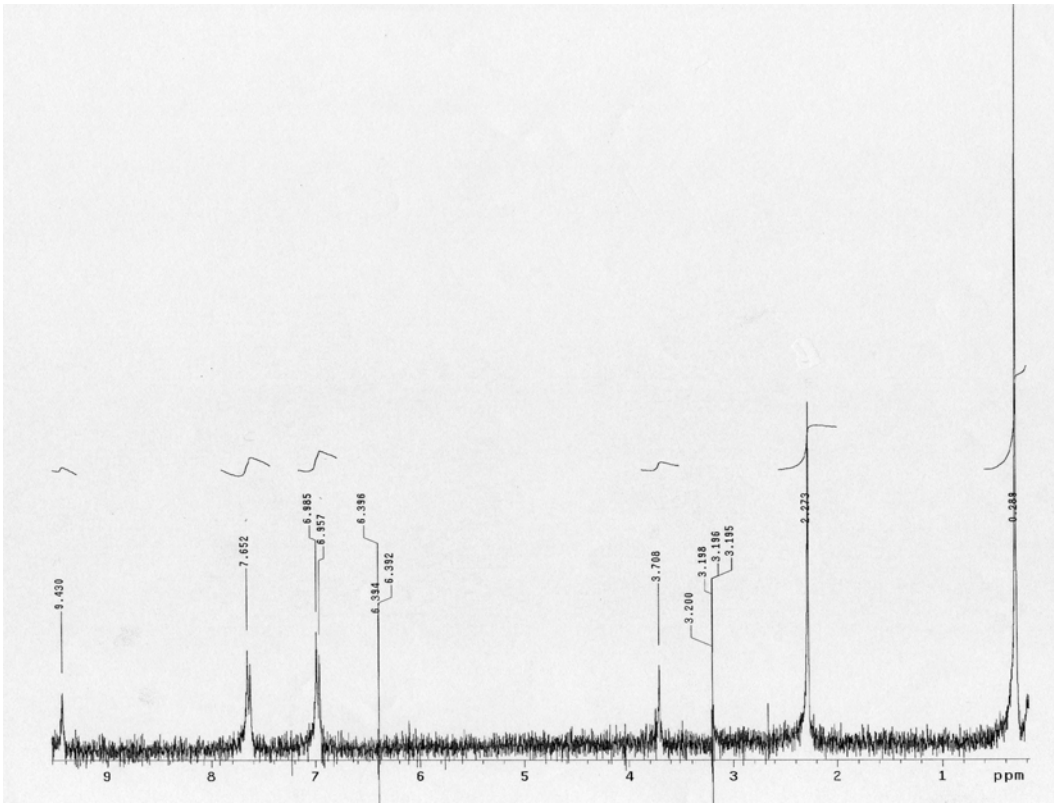


Figure SM 8.1.6 - ^{1}H NMR of *p*-hydroxyacetanilide (300 MHz, $CDCl_3$/DMSO-d_6)

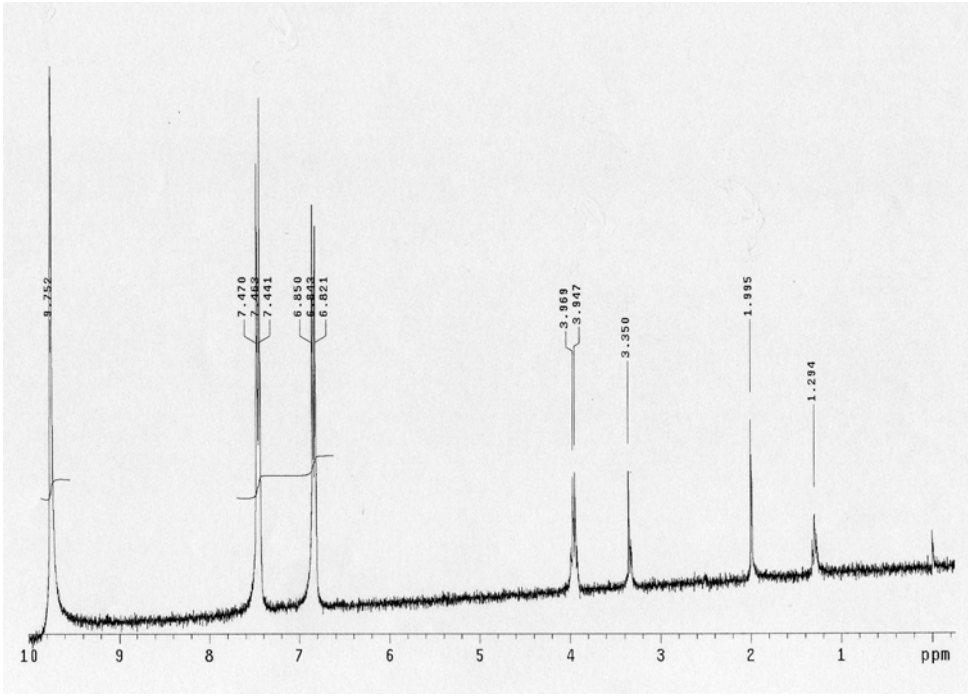


Figure SM 8.1.7 - ^{1}H NMR of phenacetin (300 MHz, DMSO-d_6)

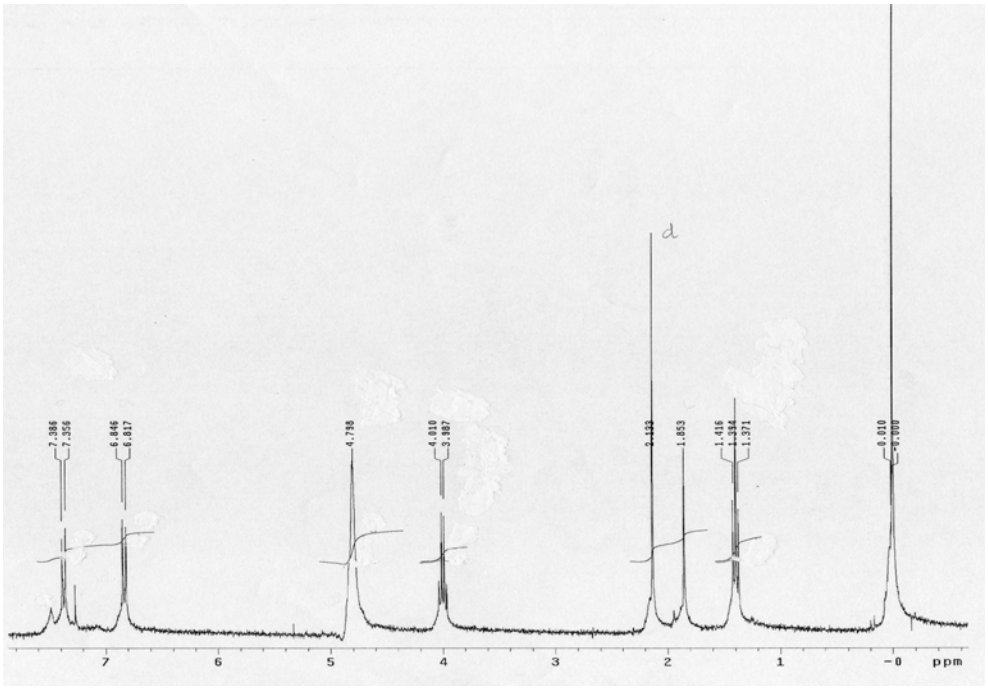


Figure SM 8.1.8 - ^{1}H NMR of dulcin (300 MHz, $CDCl_3$)

^{1}H and ^{13}C NMR spectra are available in literature (SDBS nº 3290, nº 1413).[11,12]

[1] B. D. Williams, B. Williams and L. Rodino, *J. Chem. Ed.*, 2000, **77**, 357.

[2] T. W. G. Solomons, *Organic Chemistry*, Jonh Wiley& Sons Inc., 7th ed., 1998, 837.

[3] T. W. G. Solomons, *Organic Chemistry*, Jonh Wiley& Sons Inc., 7th ed., 1998, 1026.

[4] T. W. G. Solomons, *Organic Chemistry*, Jonh Wiley& Sons Inc., 7th ed., 1998, 840.

[5] J. March, *Advanced Organic Chemistry*, Jonh Wiley and Sons, 4th ed., 1992, 903.

[6] *Handbook of Chemistry and Physics*, CRC Press,1st Student Ed., C-111.

[7] A.I. Vogel, *Vogel's Textbook of Practical Organic Chemistry*, Longman Scientific and Technical, 5th ed. 1989, 985.

[8] *Handbook of Chemistry and Physics*, CRC Press,1st Student Ed., C-46.

[9] V. T. Lieu*, J. Chem. Educ.*, 1971, **48**, 478.

[10] Handbook of Chemistry and Physics, CRC Press,1st Student Ed., C-540.

[11] URL: http://sdbs.db.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi, access in May 2015.

[12] Y. Asabe and Y. Tsuzuki*, Bull. Chem. Soc. Jpn.*, 1971, **44**, 3482.

Microwave-Assisted Solid-Phase Synthesis of Hydantoins

Supplementary Material

I. Background on the experiment topic:

We believe the explanations given about microwave assisted chemistry in the Background section of the Experiment document are sufficient to get a good grasp of that topic. If need be, the different references mentioned in the text - including recent reviews - can be consulted as well for a thorough knowledge of the subject.

In order to introduce the topic of solid-phase synthesis to students, the instructor could present in the beginning of the first session the original publication made by Robert Bruce Merrifield in 1963 where this strategy has been used for the first time.[1] The instructor could also insist on the fact that the Nobel Prize was awarded to Merrifield in 1984 for this discovery.

Concerning the topic of hydantoins, so many uses and preparations can be found in the literature that a brief summary is irrelevant. Although being out of date in terms of synthesis, the instructor can familiarize itself with their history and their main properties by reading Ware's review on the chemistry of hydantoins.[2] We also strongly suggest that the instructor becomes familiar with the Bucherer-Bergs reaction for the synthesis of hydantoin skeletons, as it is the expected answer to question 5 in the Experiment document.

II. Notes for the instructor

This experiment was made with students in their second year of Masters degree. Although we reckon that this experiment could be made with students in their first year of Masters degree, the instructor has to keep in mind that hazardous chemicals are involved which might not be suited for inexperienced students. Classically, students are divided by groups of two - working with one resin - or three - working with two resins. Depending on the microwave apparatus (*i.e.* if it can run more than one reaction at a time), more resins can be used. As the reactions involving microwave heating clearly are the limiting step in terms of time, no more than ten students should perform this experiment at the same time if the microwave apparatus can only run one sample at a time in order to match the expected duration.

This experiment is intended to undergraduate students with good general knowledge in organic chemistry. Even though all the steps are easy to understand in terms of reactivity and mechanisms, students are expected to know the mechanism of the acidic deprotection of -Boc groups and of the basic deprotection of -Fmoc groups as well as the mechanism of the Kaiser test, all of which can be easily found in the literature (supplementary information available free of charge).[3] Depending on the level of the students, Baldwin's rules for cyclisation as well as Thorpe-Ingold effect can be discussed.

This will bring a partial answer to question 6 about the feasibility of such cyclisations for large and small rings (> 6-membered rings and <5-membered rings respectively) in terms of kinetics and thermodynamics. Relationships between the polarity of the solvents and the behaviour of the resins can also be discussed. Since polystyrene-based resins are overall apolar, an apolar solvent such as DCM will provoke a swelling of the resin while polar solvents such as EtOH will induce a shrinking.

Few tricks are needed for this experiment. We suggest to wait 5 minutes after addition of solvents to the resins during the washing process before filtrating it. This will give time to the beads to properly swell / shrink. Kaiser tests can be realised by two method, either by heating in an oil bath at 130 °C (preferable) or by heating with a heat gun. If the heat gun option is chosen, students will have to be really cautious, as a strong heating can provoke a rapid boiling of the solvent and a sudden burst of the test tube. Also, gentle heating is mandatory since a strong heating can burn the beads, leading to a false positive test.

This experiment can be done in one session as well. Ideally, if it starts at 8 am, the cyclative-cleavage can be set up at 12.30 allowing the students to go on lunch break during the heating step. Depending on the apparatus, one session of 3 to 4 h can be enough if the microwave device can run multiple samples at the same time. In order to shorten the sessions, the instructor can be in charge of the vacuum evaporation of the different filtrates and of the preparation of the different NMR samples.

As stated in the Experiment manuscript, all these reactions can be performed in traditional glassware such as round-bottom flasks. However, best results are obtained when using capped propylene syringe equipped with a frit inside or a special reactor for solid-phase synthesis (Figure SM 8.2.1). This will allow a mechanical agitation, better suited for fragile resins than magnetic stirring.

<u>Supplementary description of the material requested for the laboratory session 1:</u>

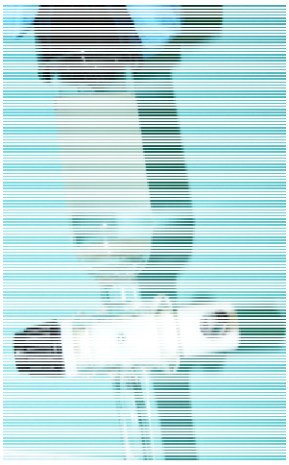
A reactor could be a capping propylene syringe equipped with a frit inside or a special reactor for solid-phase synthesis (Figure SM 8.2.1).

An orbital shaker could be also replaced by a motor equipped with a vertical rotating tray on which syringe are attached with elastics. Otherwise, a stir bar could be basically attached around syringes with an elastic to allow gentle orbital rotations on a magnetic stirring plaque (Figure SM 8.2.2).

Regarding the Kaiser test a positive and negative test are represented on Figure SM 8.2.3.

A. Syringe containing resin swelling in DCM.

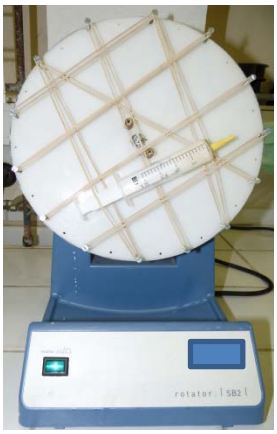
B. Syringe containing resin retracting in MeOH.



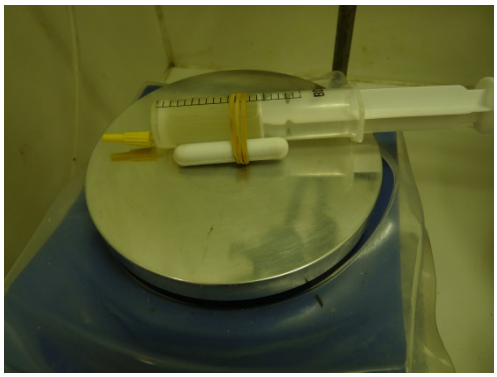
C. Solid-phase reactor containing resin swelling in DCM.

Figure SM 8.2.1. Example of reactors models which could be used for laboratory session 1.

Classically, an orbital shaker is used for this type of agitation. However, it could be replaced by a motor equipped with a vertical rotating tray on which syringe are attached with elastics. Otherwise, a stir bar could be basically attached around syringes with an elastic to allow gentle orbital rotations on a magnetic stirring plaque (Figure SM 8.2.2).



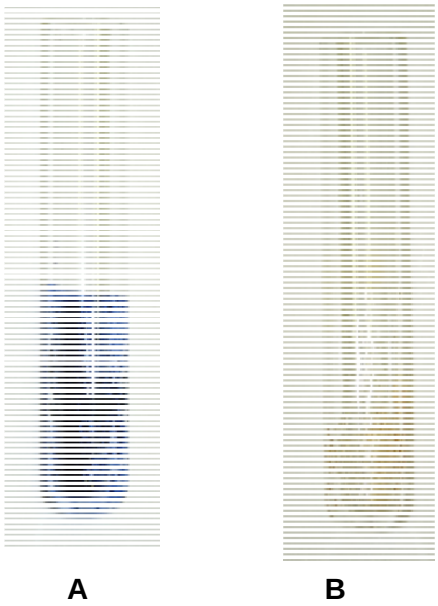
A. Orbital shaker with a vertical rotating tray.



B. Artisanal orbital shaker with a stir bar attached around the syringe.

Figure SM 8.2.2. Orbital shakers.

Regarding the Kaiser test, a positive and a negative test are represented on Figure SM 8.2.3.

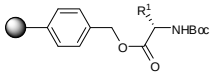
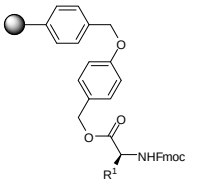
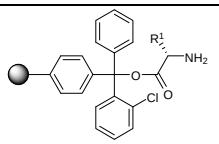
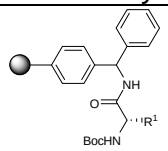
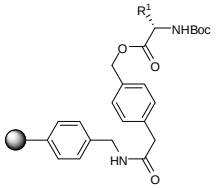
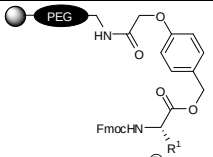


A **B**

Figure SM 8.2.3. A. Positive Kaiser test. **B.** Negative Kaiser test.

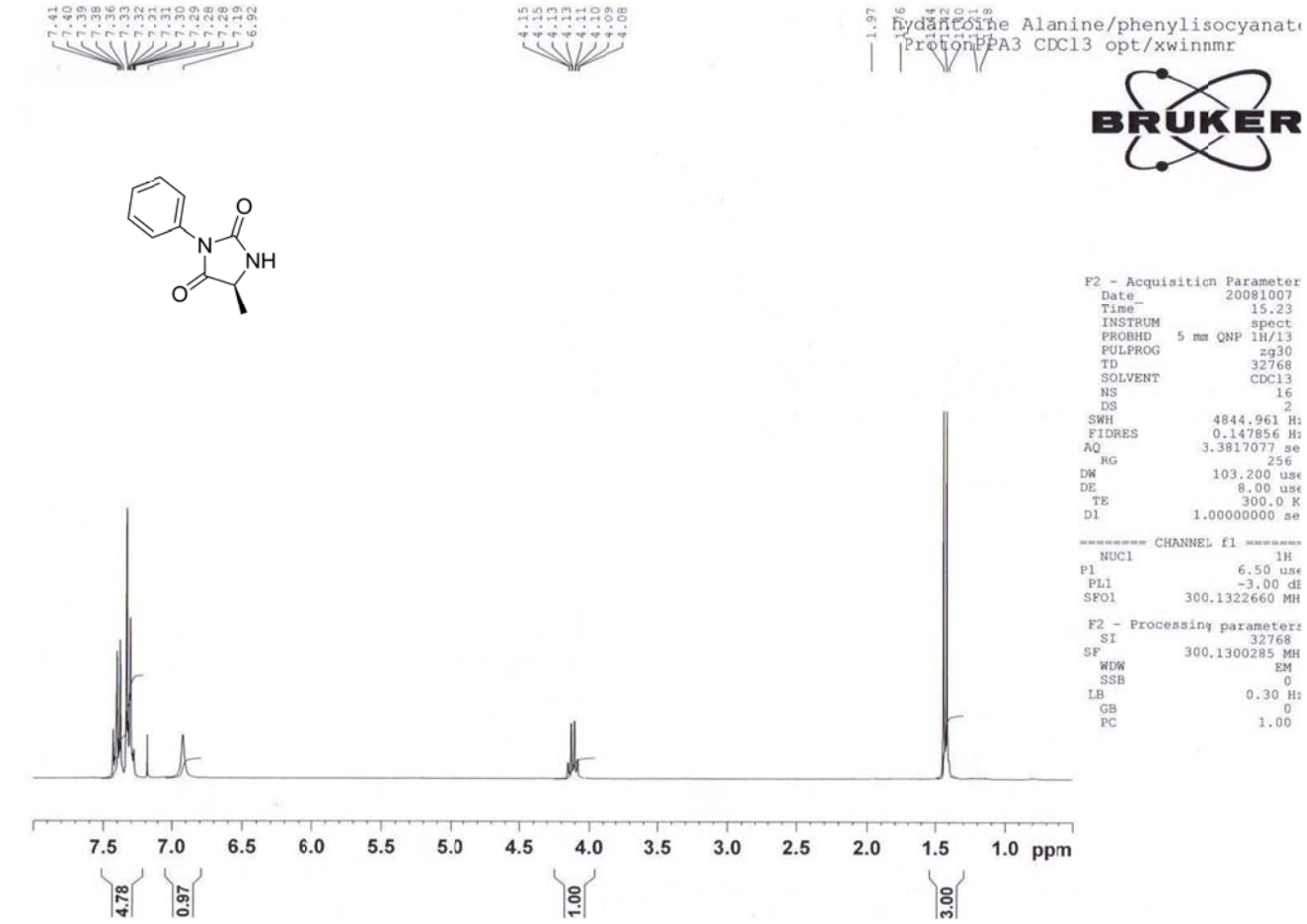
This procedure has been tested on many different amino acids and resins; yields are summarized below (Table SM 8.2.1). Note that the students usually obtain yields decreased by 20% compared to the ones given in the table.

Table SM 8.2.1. Experimental yields of hydantoins produced via a cyclative cleavage strategy.

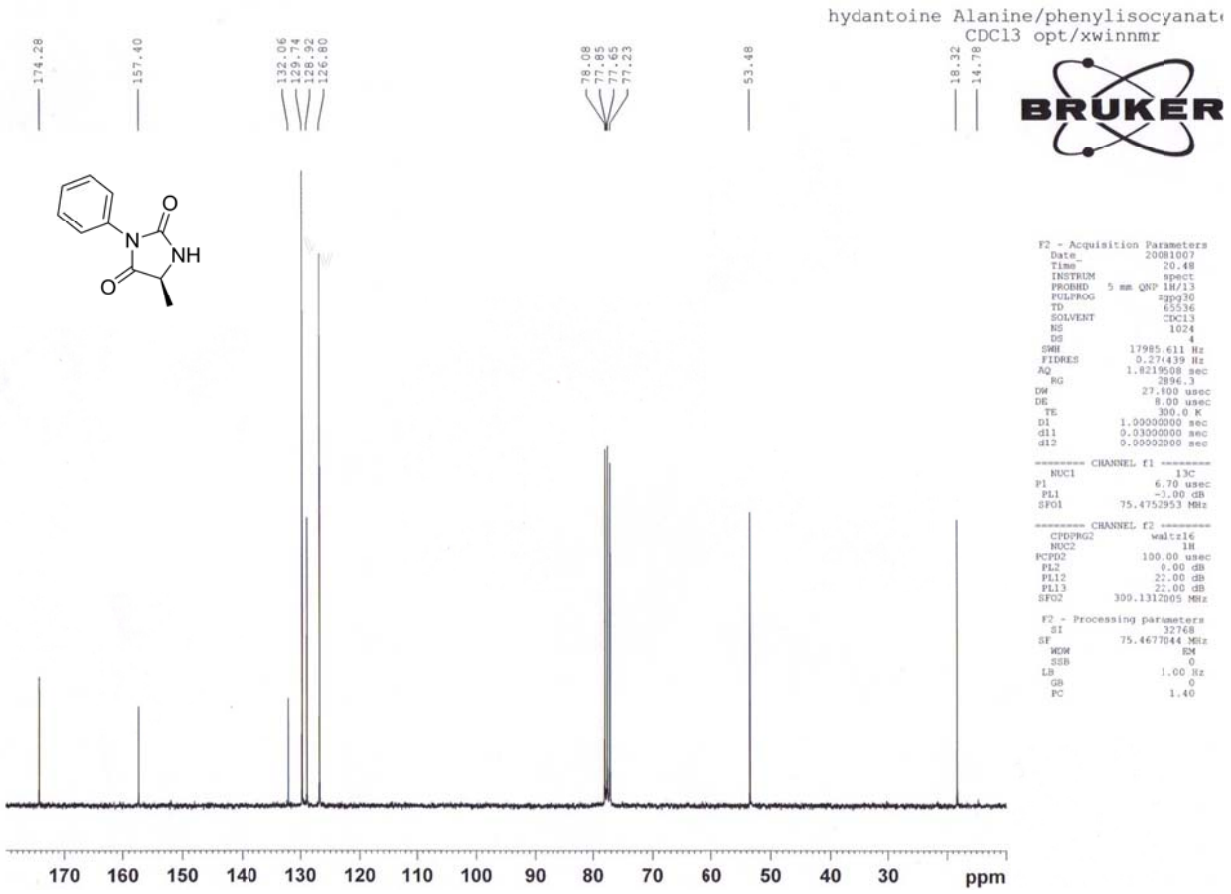
Resin with Linker	R^1	R^2	Yield %[a]
 Boc-aa-Merrifield resin	CH_2Ph	Ph	95
	CH_2Ph	H	90
	$(CH_2)_2CO_2Bz$	Ph	85
	$CH(CH_3)CH_2CH_3$	Ph	80
	CH_3	Ph	90
	iPr	Ph	75
 Fmoc-aa-Wang resin	CH_2Ph	Ph	100
	CH_2Ph	H	90
	H	Ph	70
	$CH(CH_3)CH_2CH_3$	Ph	85
	Proline	Ph	90
	$(CH_2)_2CO_2t$Bu	Ph	95
	$(CH_2)_2CO_2t$Bu	H	90
	iPr	Ph	80
	$CH_2CH(CH_3)_2$	Ph	75
	CH_3	Ph	75
 aa-2-Chloro-Trityl resin	Proline	Ph	90
	$(CH_2)_2CO_2t$Bu	Ph	75
 Boc-aa-MBHA resin	CH_3	Ph	10
 Boc-aa-PAM resin	CH_3	Ph	60
 Fmoc-aa-NovaSyn® TGA resin	$(CH_2)_2CO_2t$Bu	Ph	40

As an example, a complete set of data (^{1}H and ^{13}C NMR spectra and LC-MS spectrum) is provided below for the hydantoin synthesized from Boc-alanine Merrifield resin, using phenylisocyanate as the isocyanate source (90% yield).

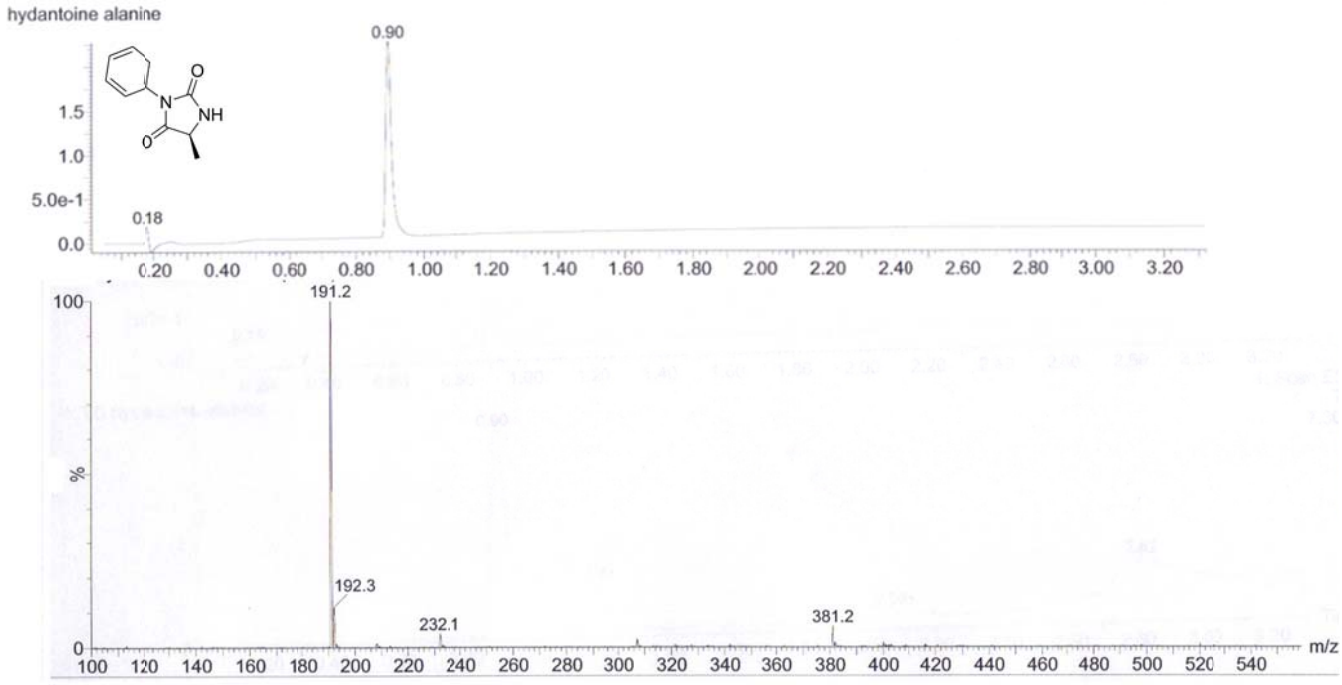
^{1}H NMR spectrum



^{13}C NMR spectrum



LC-MS spectrum



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1. R. B. Merrifield, *J. Am. Chem. Soc.*, 1963, **85**, 2149–2154.
2. E. Ware, *Chem. Rev.*, 1950, **46**, 403.
3. T. Coursindel, J. Martinez, and I. Parrot, *J. Chem. Educ.*, 2010, **87**, 640–642.