

NAME: _____ Section: A Student Number: _____

Fall 2012

Chemistry 4000 Midterm

_____/ 56 marks

- INSTRUCTIONS:
- 1) Please read over the test carefully before beginning. You should have 7 pages of questions and a periodic table.
 - 2) Unless otherwise stated in the question, explain all of your answers fully. Use diagrams where appropriate. When invoking any argument based on resonance, you must draw all relevant resonance structures.
 - 3) ALL structures must be drawn showing lone pairs, non-zero formal charges and reasonable bond angles – regardless of whether they are expanded, condensed or line-bond. Marks will be deducted for poorly drawn structures.
 - 4) Marks will be deducted for incorrect information added to an otherwise correct answer.
 - 5) If your work is not legible, it will be given a mark of zero.
 - 6) Calculators are not allowed. You are not permitted to have any electronic devices with you during the exam unless authorized by the instructor.
 - 7) You may use a molecular model kit.
 - 8) You have 2 hours to complete this test.

Confidentiality Agreement:

I agree not to discuss (or in any other way divulge) the contents of this exam until after 8:00pm Mountain Time on Monday, October 29th, 2012. I understand that breaking this agreement would constitute academic misconduct, a serious offense with serious consequences. The minimum punishment would be a mark of 0/56 on this exam; the maximum punishment would include expulsion from this university.

Signature: _____

Date: _____

Course: CHEM 4000A (Medicinal Chemistry)

Semester: Fall 2012

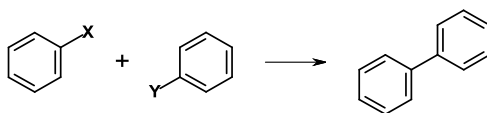
The University of Lethbridge

Question Breakdown

Q1	/ 7
Q2	/ 4
Q3	/ 4
Q4	/ 6
Q5	/ 6
Q6	/ 6
Q7	/ 8
Q8	/ 15

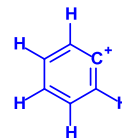
Total	/ 56
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1. You wish to perform the following reaction: [7 marks]



- (a) Why can you not use an S_N1 approach? [2 marks]

An S_N1 approach would require formation of an aryl carbocation:
Aryl carbocations are highly unstable.



- (b) Why can you not use an S_N2 approach? [2 marks]

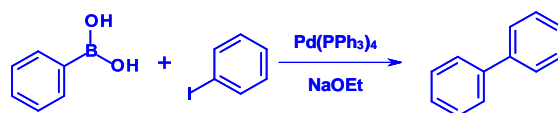
S_N2 reactions require the nucleophile to attack 180° from the leaving group. Here, that would require the nucleophile to travel through the middle of the benzene ring.

More generally, S_N2 reactions can only be performed at tetrahedral electrophilic sites.

- (c) How would you do it? Include specific groups to replace X and Y, and identify any other necessary reagents. [3 marks]

Two reasonable options were suggested – a Suzuki approach and an organocuprate approach.

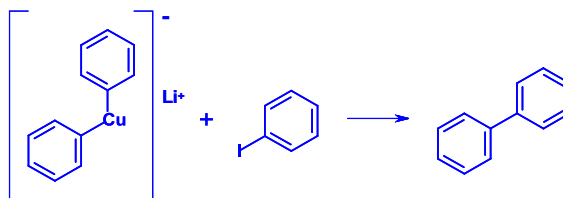
Suzuki approach:



Could also use:

- a boronate ester ($ArB(OR)_2$) instead of the borate ($ArB(OH)_2$)
- a different alkoxide, a hydroxide or a carbonate instead of the ethoxide
- a bromide or a triflate instead of the iodide
- a different Pd[0] catalyst

Organocuprate approach:



2. [4 marks]

- (a) What is meant by the term “umpolung”? [1 mark]

“Umpolung” refers to a species having inverted reactivity (i.e. the opposite of “normal”).

e.g. In a normal Diels-Alder reaction, the diene usually has electron-donating groups while the dienophile usually has electron-withdrawing groups. In an “umpolung” Diels-Alder reaction, the diene has electron-withdrawing groups while the dienophile has electron-donating groups.

- (b) Give an example of an unpoled synthon, and indicate what feature(s) make it unpoled.

Any d^1 , a^2 , d^3 or a^4 synthon is valid. The most common correct answer was CN^- . [3 marks]

The cyanide ion (CN^-) is a d^1 synthon and therefore an unpoled synthon. Usually, a carbon atom bonded to a heteroatom will be partially positive (since most heteroatoms are more electronegative than C) and therefore electrophilic. In CN^- , the carbon bonded to nitrogen has a negative charge and is therefore nucleophilic.

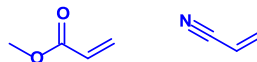
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3. Explain why an a^3 synthon is usually a better choice than a d^3 synthon. [4 marks]

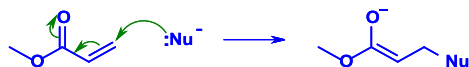
Your answer should include an example of each.

An a^3 synthon is a natural synthon while a d^3 synthon is an unpoled synthon.

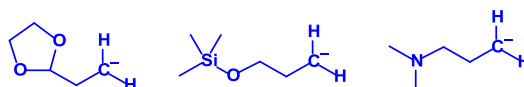
In a typical a^3 synthon, the electrophilic carbon is connected to an electronegative heteroatom via a pi system. Typical examples include:



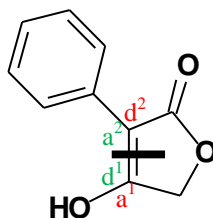
When a nucleophile attacks, the increased electron density can therefore be delocalized onto the heteroatom, stabilizing the intermediate:



To make a d^3 synthon, it is necessary to generate a carbanion (or equivalent) in the presence of a heteroatom without any stabilization from the heteroatom. This may even require protection of the functional group containing the heteroatom. Typical examples include:



4. The first synthesis we worked through in problem set was that of rofecoxib (Vioxx®). One of the key disconnections used in one of the syntheses is shown below (the thick dark line).



There are two possible pairs of synthons generated by this disconnection. [6 marks]

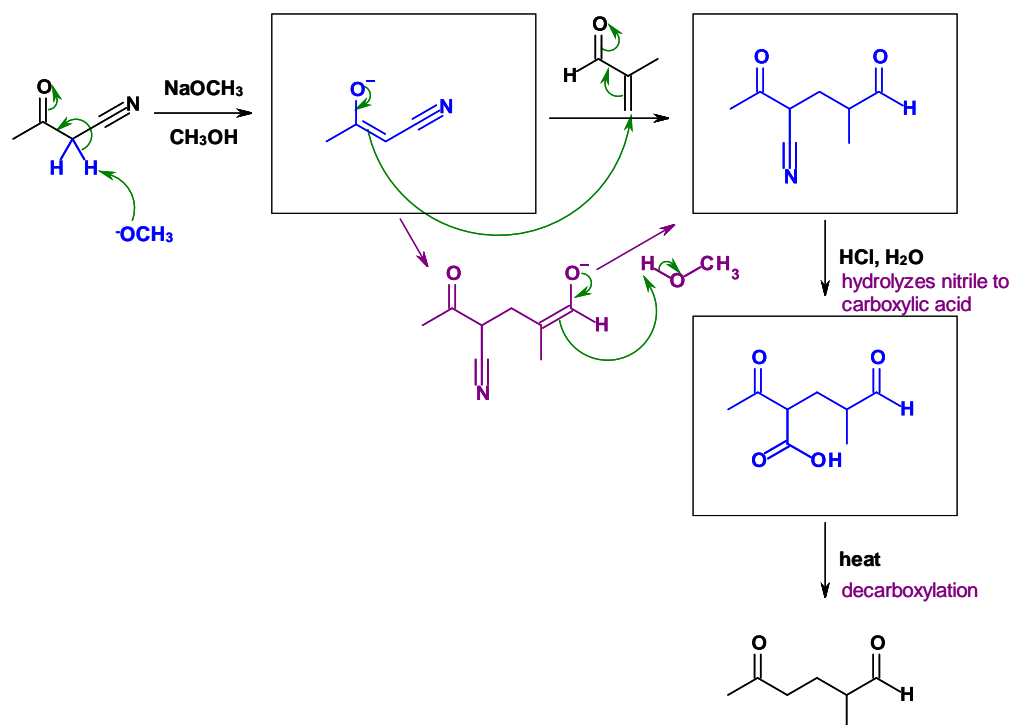
- (a) Identify each pair of synthons (clearly indicating which side of the disconnection corresponds to each synthon). [4 marks]

This disconnection either creates an a^1 synthon and a d^2 synthon (shown in red) or a d^1 synthon and an a^2 synthon (shown in green).

- (b) Which of the pairs of synthons is preferable? Why? [2 marks]

It is preferable to use an a^1 synthon and a d^2 synthon as those are both natural synthons. (d^1 and a^2 synthons are both unpoled.)

5. Consider the following sequence of reactions. [6 marks]
There is no work-up done between reactions.

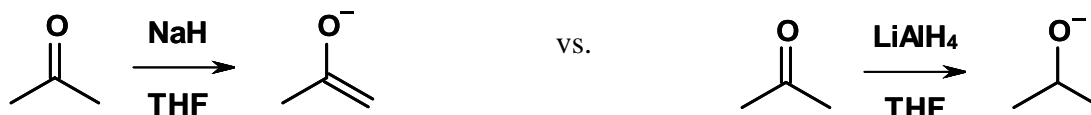


- (a) Draw the product of each step in the appropriate box. [3 marks]
 (b) What was the purpose of the $-\text{CN}$ group? [3 marks]

The nitrile served as an auxiliary functional group. It softened the nucleophilic site to favour addition at the softer electrophilic site (as shown) rather than at the harder electrophilic site (directly attacking the C of the aldehyde).

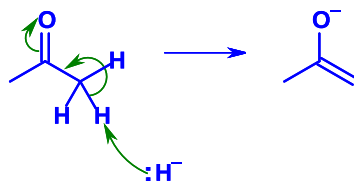
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6. Use an argument based on hard/soft principles to explain why NaH and LiAlH₄ react differently with acetone: [6 marks]

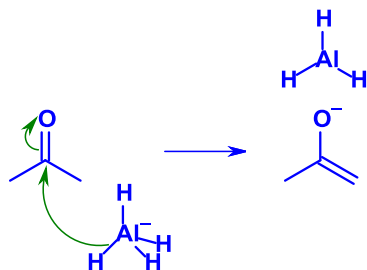


Your answer should include a mechanism for each of the reactions shown above.

Sodium hydride acts as a base, deprotonating a hydrogen α to the carbonyl:



Lithium aluminium hydride (LiAlH₄) acts as a nucleophile, attacking the carbonyl carbon:



While both nucleophiles are relatively hard, H⁻ is a harder electron donor than AlH₄⁻. Both have an overall charge of -1 and both species contain negative (or partially negative) hydrogen atoms. In H⁻, the negative charge is focused on a single hydrogen atom and the charge density of H⁻ is therefore large. In AlH₄⁻, the negative charge is shared over a much larger molecule so the charge density is much lower.

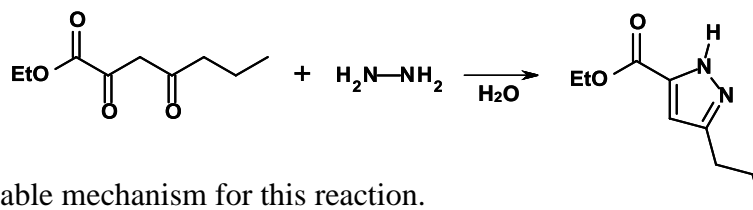
Even if we argue that H is more electronegative than Al, we would have to place a full +3 charge on the Al to give each H a -1 charge. This would not be a reasonable description of this molecule (since it would imply fully ionic bonds – the electronegativity difference is not great enough to support that proposition).

So, if H⁻ is the harder electron donor, that explains why it donates electrons to the harder electron-accepting site. While the C of the carbonyl is directly attached to O and one might expect it to bear a greater partial positive charge than the α -hydrogen, carbon atoms are significantly larger than hydrogen atoms. Hydrogen's small size means that an acidic proton will always be considered a fairly hard electron-accepting site. As such, the harder H⁻ donates electrons to the harder α -hydrogen while the softer AlH₄⁻ donates electrons to the softer carbonyl carbon. This is consistent with the observed experimental behavior.

Note that Na⁺ and Li⁺ are serving as counterions. They are not playing any significant role in the mechanism and they are therefore not relevant to the hard/soft argument.

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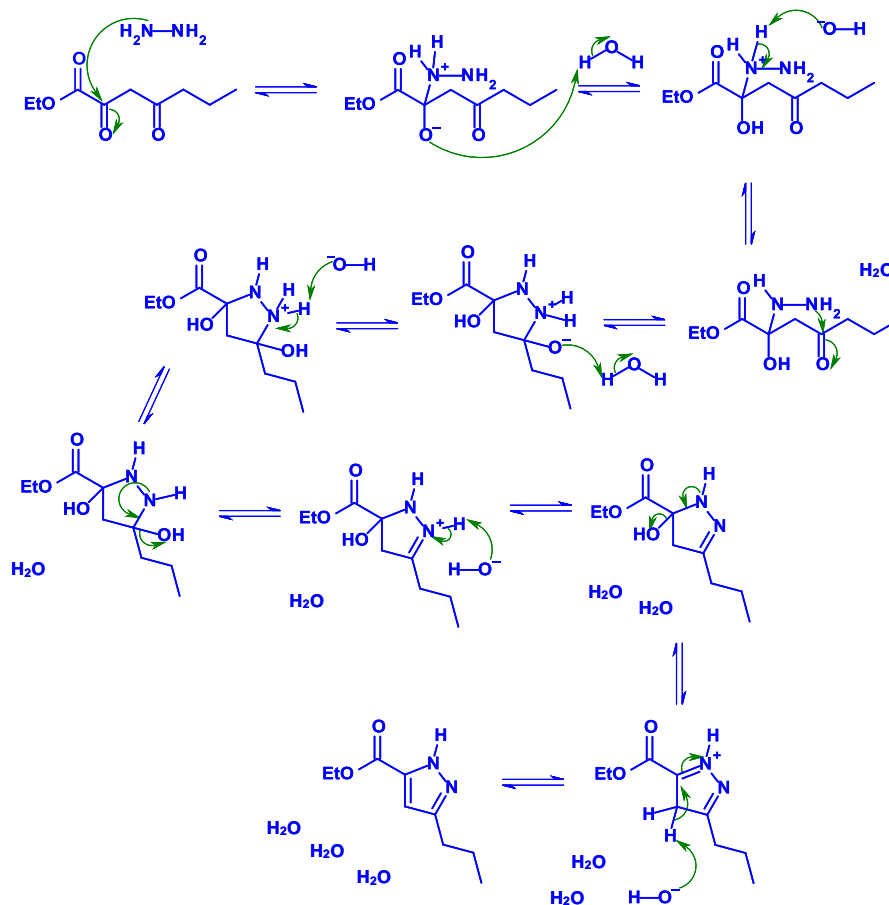
7. One of the first steps in the synthesis of sildenafil (Viagra[®]) is shown below. [8 marks]



Propose a reasonable mechanism for this reaction.

Key points worth noting:

- The electron-withdrawing ester group makes the carbon of the ketone next to it more electrophilic than the carbon of the other ketone.
- This is a mildly basic solution (water + amine), so there's no significant amount of H_3O^+ available (and NH_2NH_2 serves as a competing base which would "mop up" most H_3O^+ produced in the mechanism). As such, when there is a choice between protonating O^- and deprotonating N^+ , do the protonation first so that HO^- is made as an intermediate rather than H_3O^+ .
- Water is not a strong enough acid to protonate neutral O.
- You may not protonate O in the presence of O^- .
- If a four-atom transition state is required to transfer a proton from one atom to another, the "basic" atom "cannot reach" the proton.
- It is not necessary to continue to show all of the water molecules for the whole mechanism after they've been made. I only did so here so that you could track the atoms.



8. How would you make each of the molecules below? [15 marks]

Your answers should take the form of a retrosynthetic analysis followed by chemical equations for the reactions in the synthesis itself. Show all required reagents, and number steps within a reaction if order of addition is important.

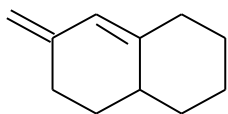
You may use any reagents that you could reasonably expect to be commercially available and that contain no more than 6 carbon atoms. (Exception: Reagents may contain one or more benzene rings in addition to the 6 carbon limit.)

If you are suggesting a multi-step synthesis, write an equation for each step.

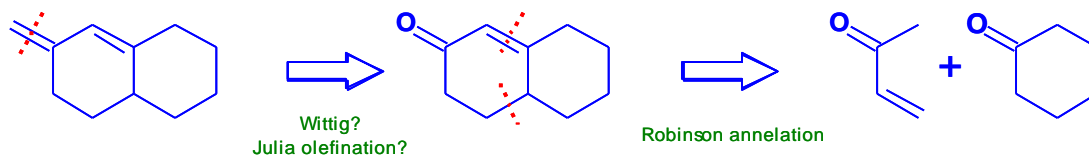
There are many possible “right answers” for each synthesis. I have included one for each.

“Reasonably expect to be commercially available” = don’t choose any starting materials containing functional groups you’ve never seen or functional groups which would react with each other (either intermolecularly or intramolecularly). e.g. In (b), a compound containing both an amine and a bromine is not a reasonable starting material.

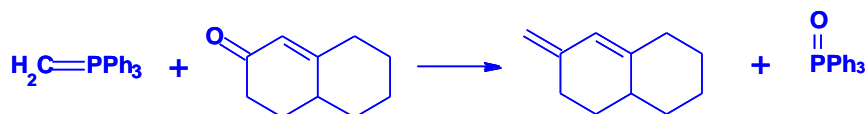
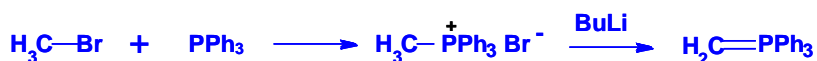
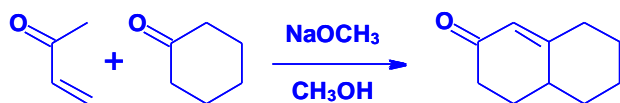
(a) [5 marks]



Retrosynthetic analysis:



One proposed synthetic route:



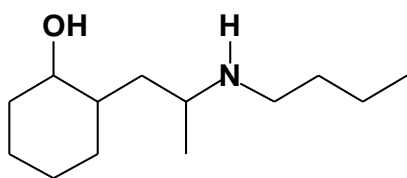
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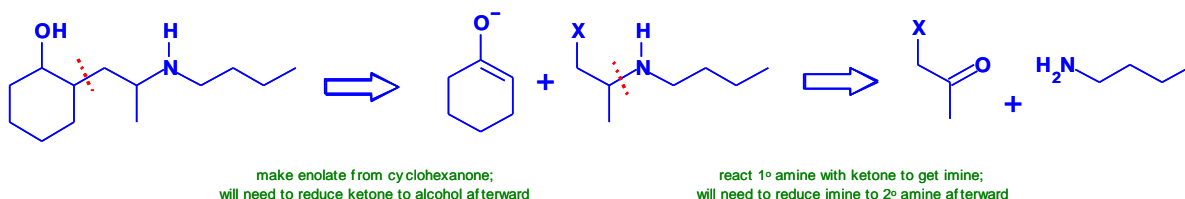
8. *continued...*

(b)

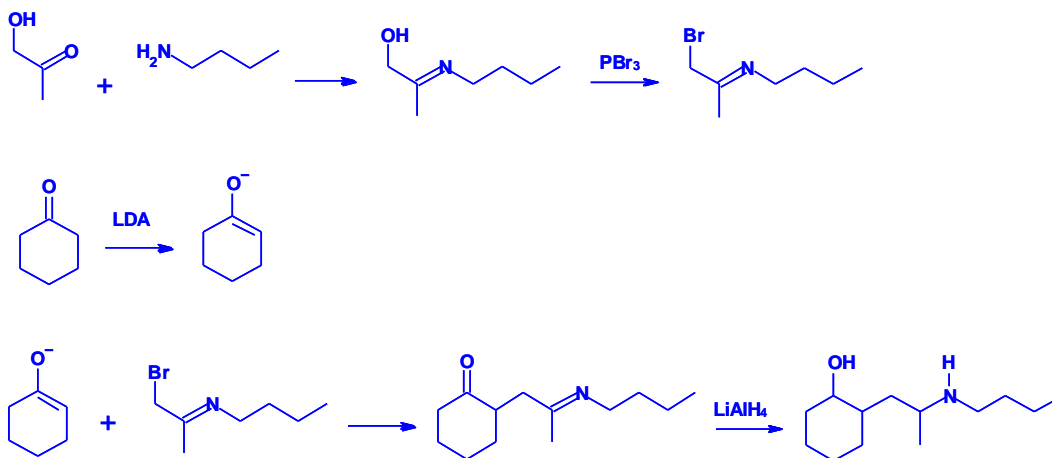


[10 marks]

Retrosynthetic analysis:



One proposed synthetic route:



Note that these steps could have been performed in a variety of different orders. The advantage of the order presented is that it does not require any protecting groups so the total number of synthetic steps is minimized.

If, for example, the enolate turned out to attack the imine competitively with the alkyl bromide, the imine could be reduced to the amine earlier, but that would add an extra synthetic step.

Also, be aware that adding amines to alkyl halides (instead of to aldehydes or ketones) is a risky proposition because each substitution makes the amine increasingly more nucleophilic. So, stopping at one addition is extremely difficult if not impossible (depending on sterics).

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1**CHEM 1000 Standard Periodic Table****18**

1.0079 H 1																4.0026 He 2	
6.941 Li 3	9.0122 Be 4											10.811 B 5	12.011 C 6	14.0067 N 7	15.9994 O 8	18.9984 F 9	20.1797 Ne 10
22.9898 Na 11	24.3050 Mg 12	3	4	5	6	7	8	9	10	11	12	26.9815 Al 13	28.0855 Si 14	30.9738 P 15	32.066 S 16	35.4527 Cl 17	39.948 Ar 18
39.0983 K 19	40.078 Ca 20	44.9559 Sc 21	47.88 Ti 22	50.9415 V 23	51.9961 Cr 24	54.9380 Mn 25	55.847 Fe 26	58.9332 Co 27	58.693 Ni 28	63.546 Cu 29	65.39 Zn 30	69.723 Ga 31	72.61 Ge 32	74.9216 As 33	78.96 Se 34	79.904 Br 35	83.80 Kr 36
85.4678 Rb 37	87.62 Sr 38	88.9059 Y 39	91.224 Zr 40	92.9064 Nb 41	95.94 Mo 42	(98) Tc 43	101.07 Ru 44	102.906 Rh 45	106.42 Pd 46	107.868 Ag 47	112.411 Cd 48	114.82 In 49	118.710 Sn 50	121.757 Sb 51	127.60 Te 52	126.905 I 53	131.29 Xe 54
132.905 Cs 55	137.327 Ba 56	La-Lu	178.49 Hf 72	180.948 Ta 73	183.85 W 74	186.207 Re 75	190.2 Os 76	192.22 Ir 77	195.08 Pt 78	196.967 Au 79	200.59 Hg 80	204.383 Tl 81	207.19 Pb 82	208.980 Bi 83	(210) Po 84	(210) At 85	(222) Rn 86
(223) Fr 87	226.025 Ra 88	Ac-Lr	(261) Rf 104	(262) Db 105	(263) Sg 106	(262) Bh 107	(265) Hs 108	(266) Mt 109	(281) Dt 110	(283) Rg 111							

138.906 La 57	140.115 Ce 58	140.908 Pr 59	144.24 Nd 60	(145) Pm 61	150.36 Sm 62	151.965 Eu 63	157.25 Gd 64	158.925 Tb 65	162.50 Dy 66	164.930 Ho 67	167.26 Er 68	168.934 Tm 69	173.04 Yb 70	174.967 Lu 71
227.028 Ac 89	232.038 Th 90	231.036 Pa 91	238.029 U 92	237.048 Np 93	(240) Pu 94	(243) Am 95	(247) Cm 96	(247) Bk 97	(251) Cf 98	(252) Es 99	(257) Fm 100	(258) Md 101	(259) No 102	(260) Lr 103

Developed by Prof. R. T. Boeré