

Tetramethyl Orthosilicate (TMOS) as a Reagent for Direct Amidation of Carboxylic Acids

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Dial-a-Molecule Annual Meeting: Enabling Synthesis 10th July 2018
iHub, White City Campus, Imperial College London

A word cloud visualization representing research interests in synthetic chemistry. The most prominent words are 'synthesis', 'reaction', and 'data'. Other significant terms include 'chemical', 'new', 'available', 'development', 'equipment', 'important', 'methods', 'catalysts', 'optimisation', 'term', 'design', 'outcomes', and 'processes'. The size of each word indicates its relative frequency or importance across the dataset.

from Dial-A-Molecule Roadmap:

<http://generic.wordpress.soton.ac.uk/dial-a-molecule/wp-content/blogs.dir/sites/50/2012/10/Dial-a-Molecule-Roadmap.pdf>

Amides

Bioactive Natural products

- Penicillins
- Ciclosporin
- Capsaicin
- Echinacea



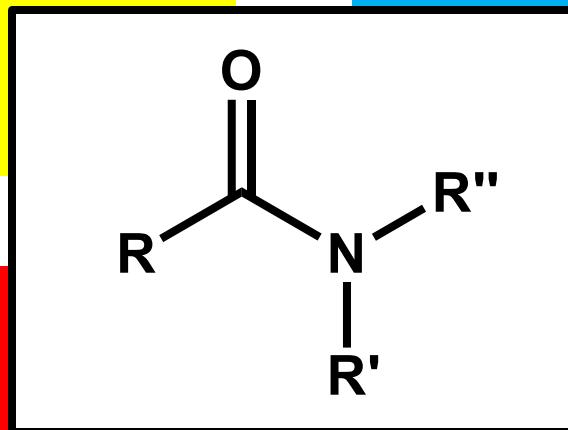
Pharmaceuticals

- Lipitor
- Lidocaine
- Nicorandil
- Atazanavir
- Imatinib



Polymers

- Kevlar
- Aramid
- Nylons
- Tennis rackets
- Brakes



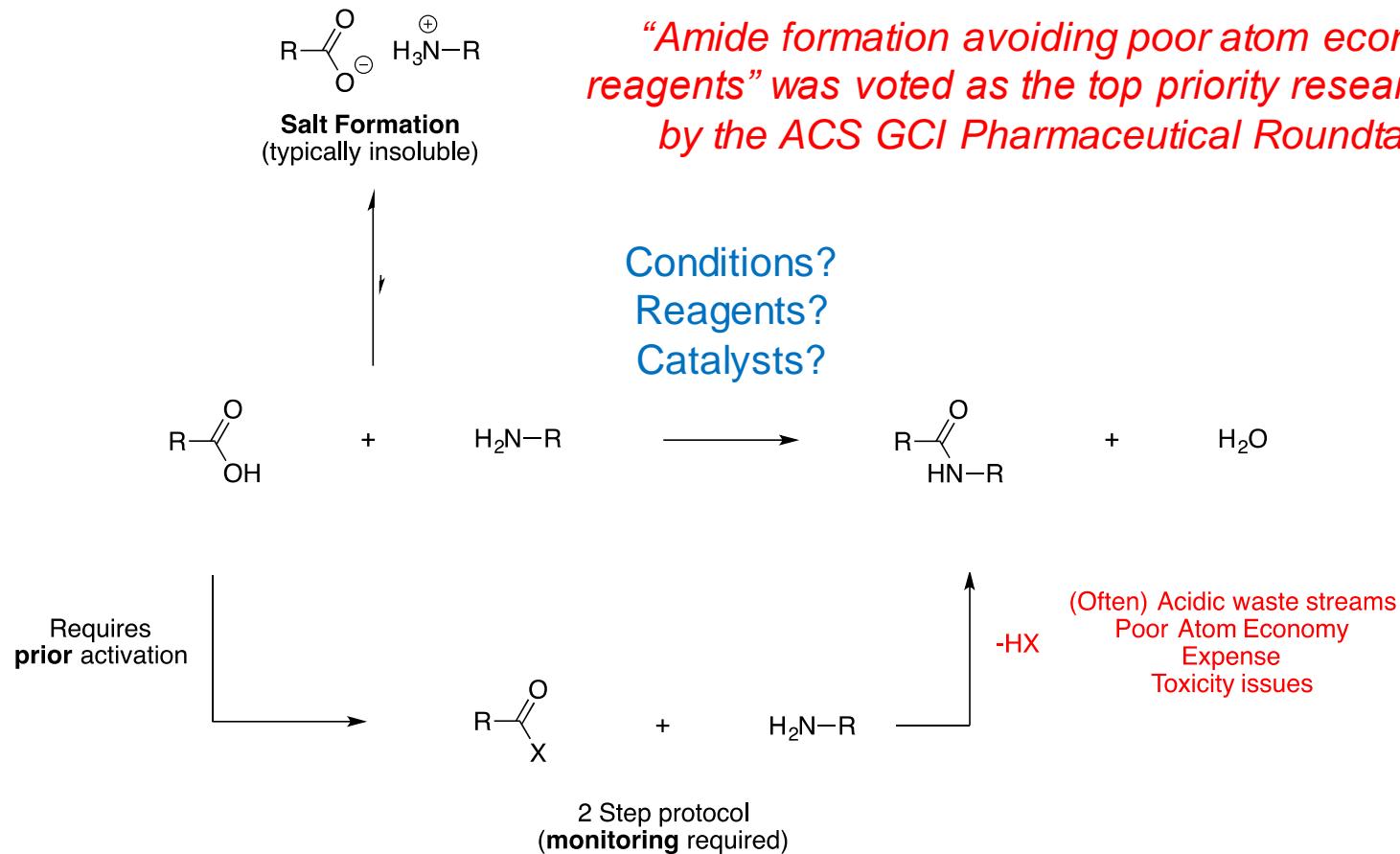
Peptides

- Proteins
- Enzymes
- Spider silk
- Hair



Amide bond linkages are present in ca. 25% of top 200 selling pharmaceuticals (and in 60% of all newly approved drugs in 2017).

Direct Amidations

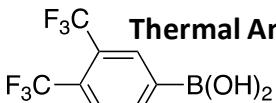


aliphatic carboxylic acid + aromatic carboxylic acid + Aniline +

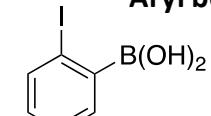
Direct Amidations in the Literature

2° amine 2° amine 2° amine 2° amine 2° amine RCO₂H ArCO₂H

Thermal Amidations



Yamamoto 1996
Aryl boronic acids



Hall 2008
Boronates

B(OCH₂CF₃)₃ **Sheppard 2016**

Boric acid

B(OH)₃ **Tang 2005**

Group IV metals

Cp₂HfCl₂ **Adolfsson 2015**

Miscellaneous
(homogeneous)

Mukaiyama (+ others)

Silica Gels

Other heterogenous



The Pharmacat Consortium & A Collaboration

Imperial College London

The Pharmacat Consortium

Welcome to the Pharmacat Consortium



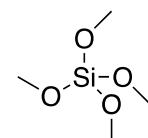
GlaxoSmithKline



Dr Steve Fussell



Professor Paul Lickiss
Department of Chemistry
Imperial College London



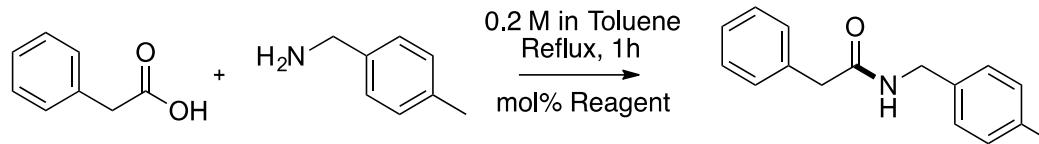
Tetramethylorthosilicate
(TMOS)

Direct Amidations with Tetraalkoxysilanes as Overlooked Reagents

Tetramethylorthosilicate (TMOS)	Tetraethylorthosilicate (TEOS)
$\begin{array}{c} \text{OMe} \\ \\ \text{MeO}-\text{Si}-\text{OMe} \\ \\ \text{OMe} \end{array}$	$\begin{array}{c} \text{OEt} \\ \\ \text{EtO}-\text{Si}-\text{OEt} \\ \\ \text{OEt} \end{array}$
b.p. 121 °C	b.p. 168 °C
\$14 per mole	\$5 per mole

These compounds react slowly with water at neutral pH but more rapidly in acidic conditions and even more so in basic solution. They can be stored without special precautions and handled in air without significant hydrolysis.

Aliphatic acid + primary amine
'Class: Al-1°'



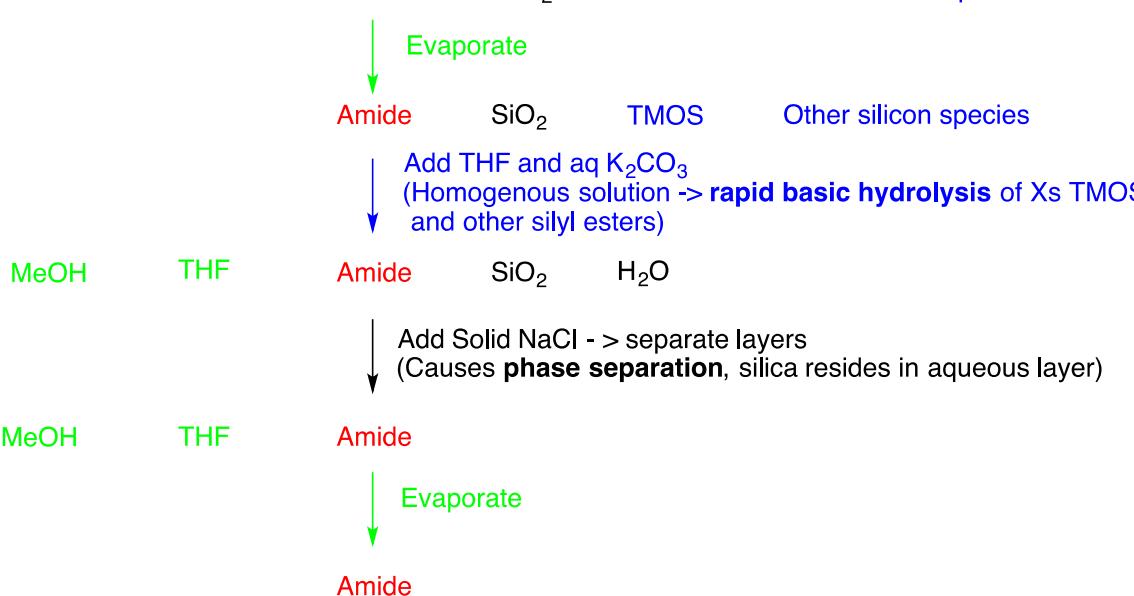
Entry	Reagent	mol%	%Conversion
1	-	-	11
2	TEOS	25	45
3	TEOS	100	70
4	TEOS	200	85
5	TMOS	25	55
6	TMOS	100	77
7	TMOS	200	100 (100) ^a

The amide product is obtained in pure form directly after work-up

Direct Amidations with Tetraalkoxysilanes: The Work-up



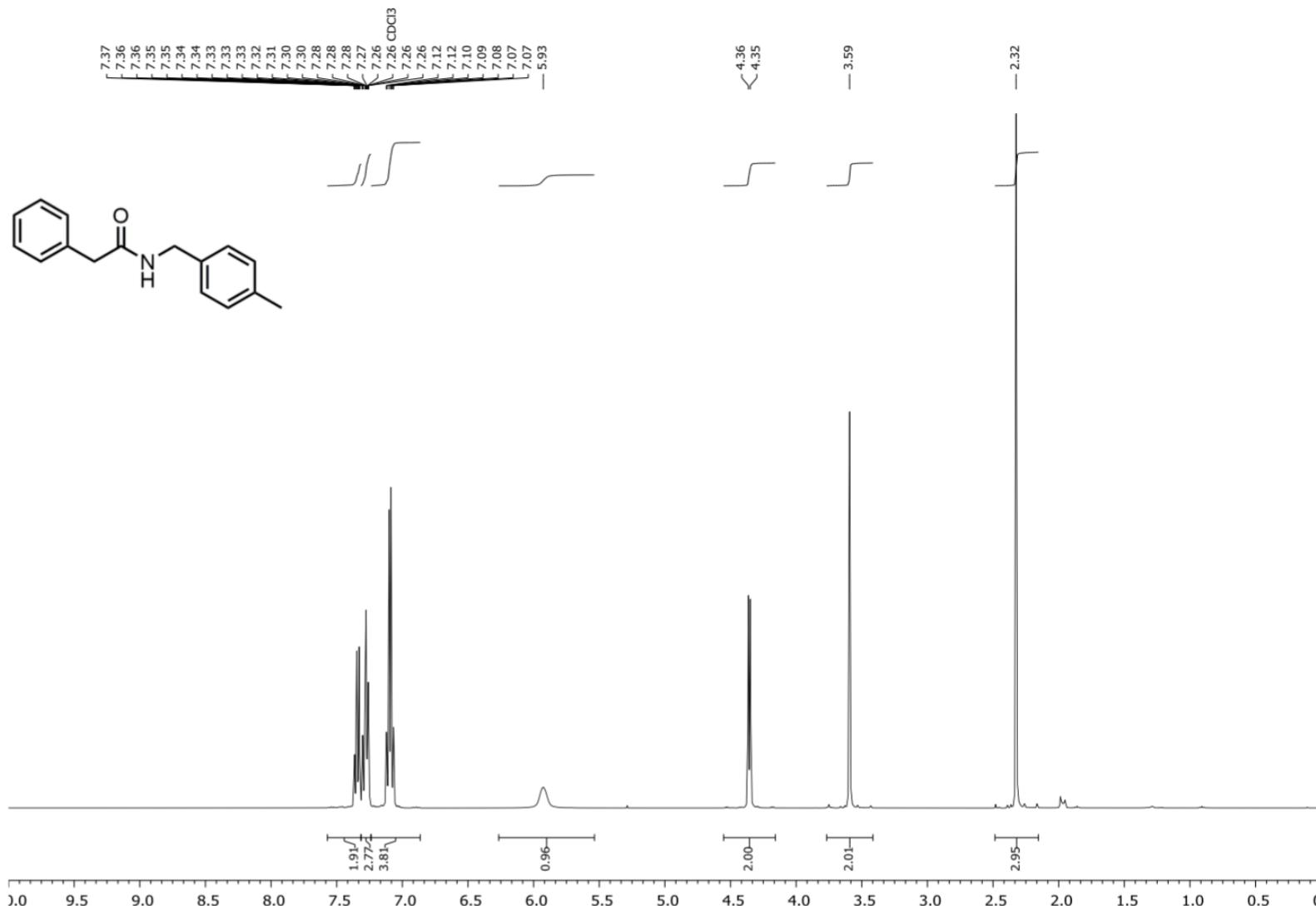
At complete conversion: MeOH Toluene Amide SiO₂ TMOS Other silicon species



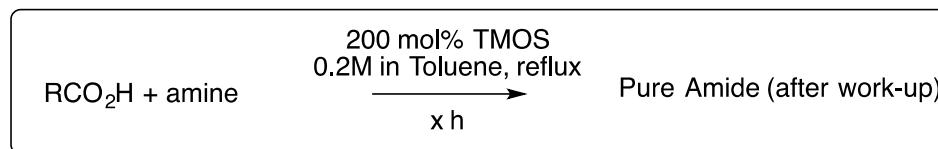
The work-up procedure provides the amides directly in pure form
even for incomplete amidations:

- Unreacted carboxylic acid removed by basic wash;
- Aq. HCl wash can be applied to remove unreacted aliphatic amines.

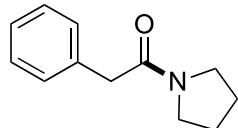
‘Crude’ Products are Pure!



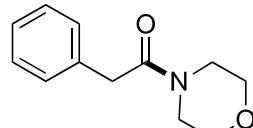
Direct Amidations of Aliphatic Carboxylic Acids with TMOS



Aliphatic acid + cyclic secondary amines
'Class: Al-c2°'

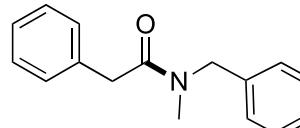


98%
(1h)



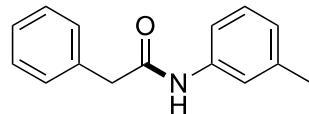
96%
(2h)

Aliphatic acid + acyclic secondary amine
'Class: Al-a2°'



81%
(11h)

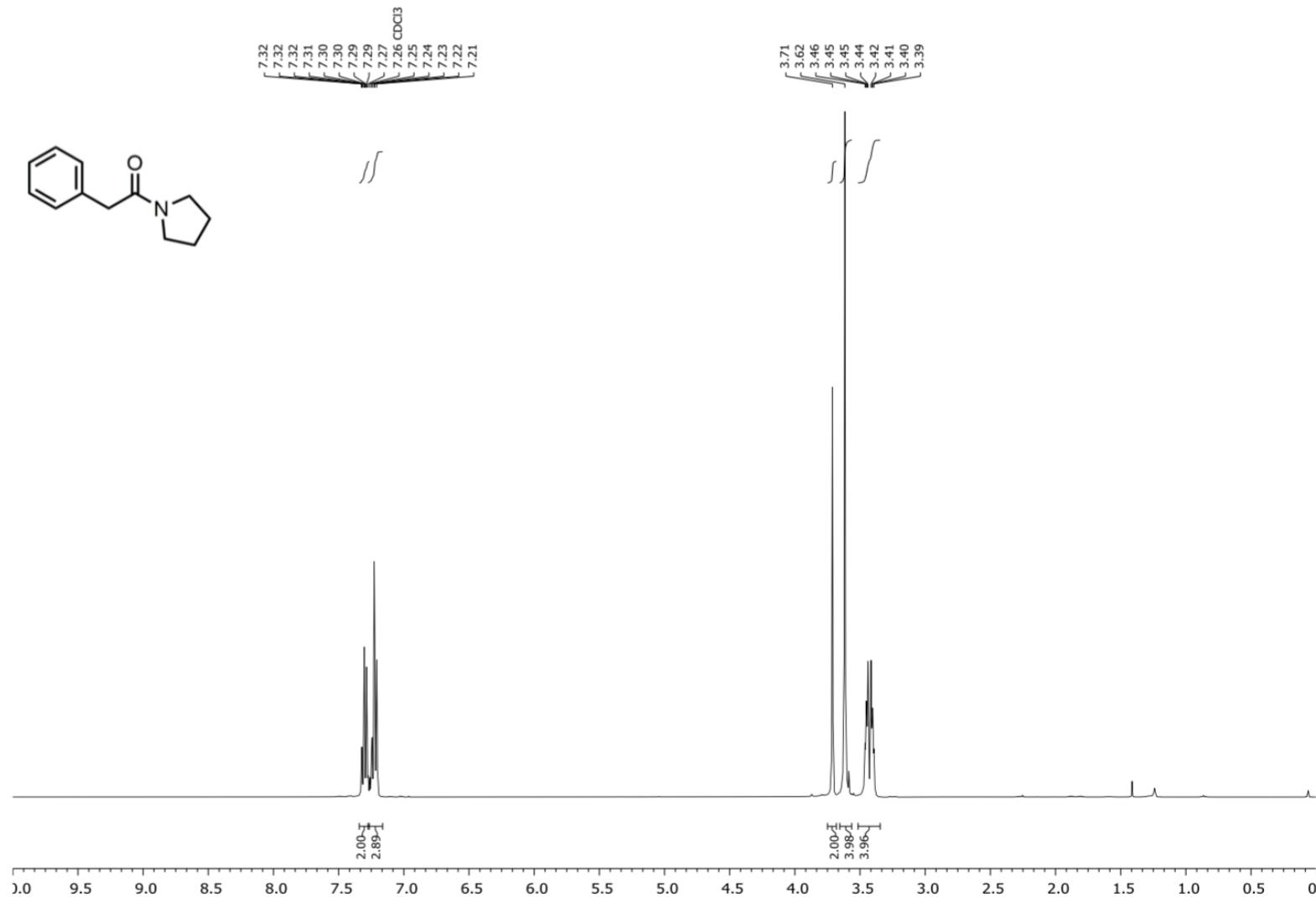
Aliphatic acid + aniline
'Class: Al-An'



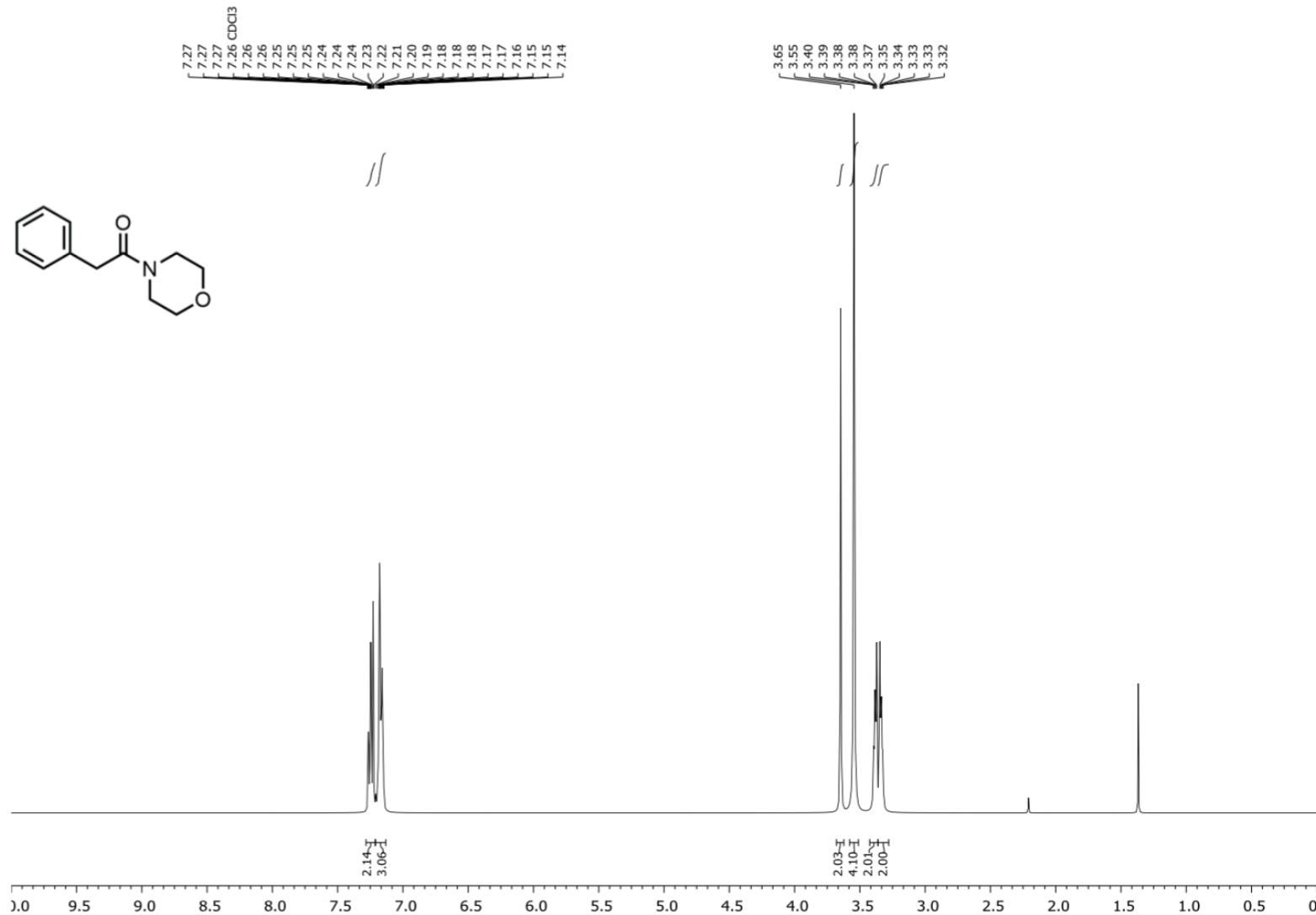
84%
(7h)

250 mol% TMOS, 0.5M

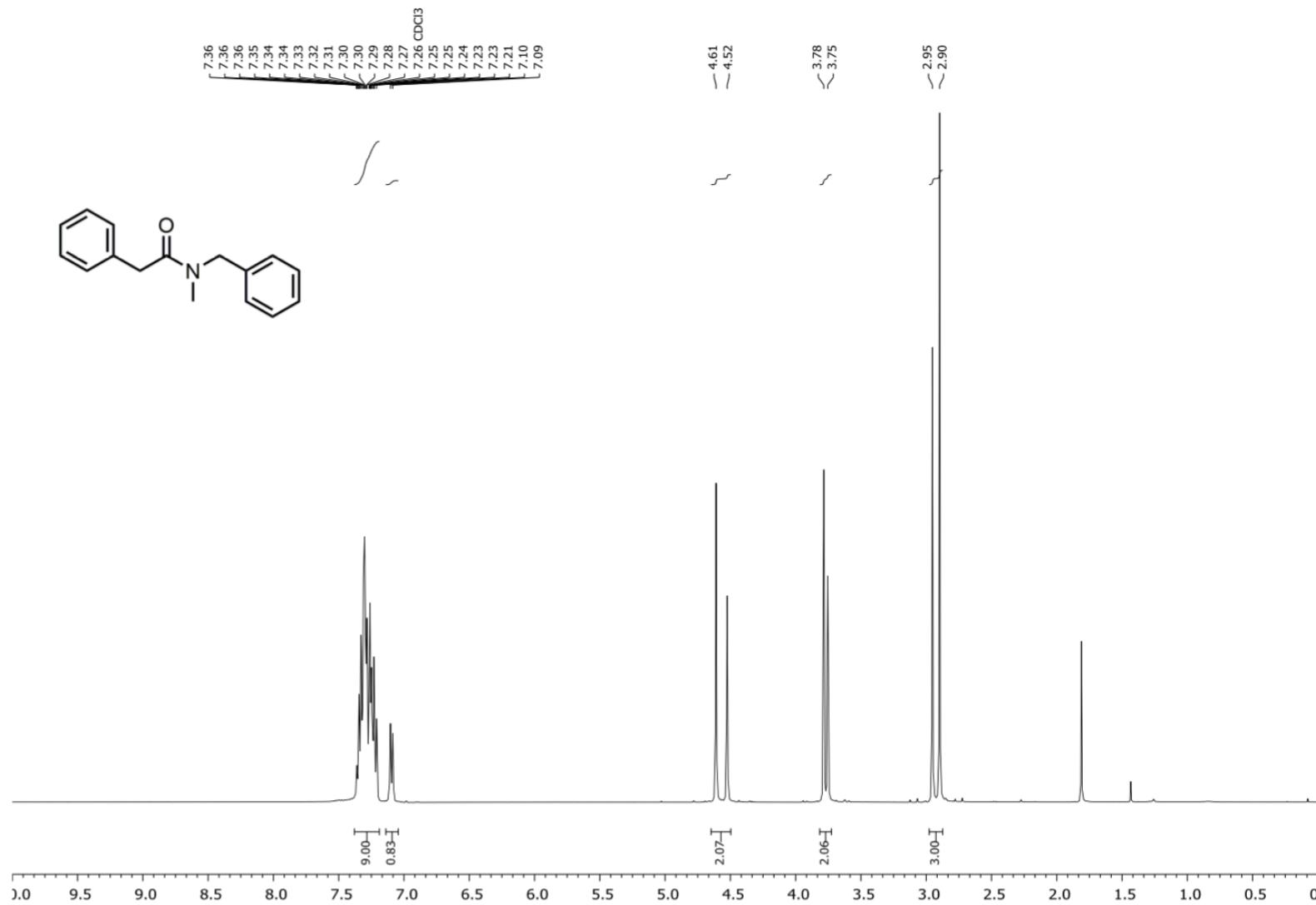
‘Crude’ Products are Pure!



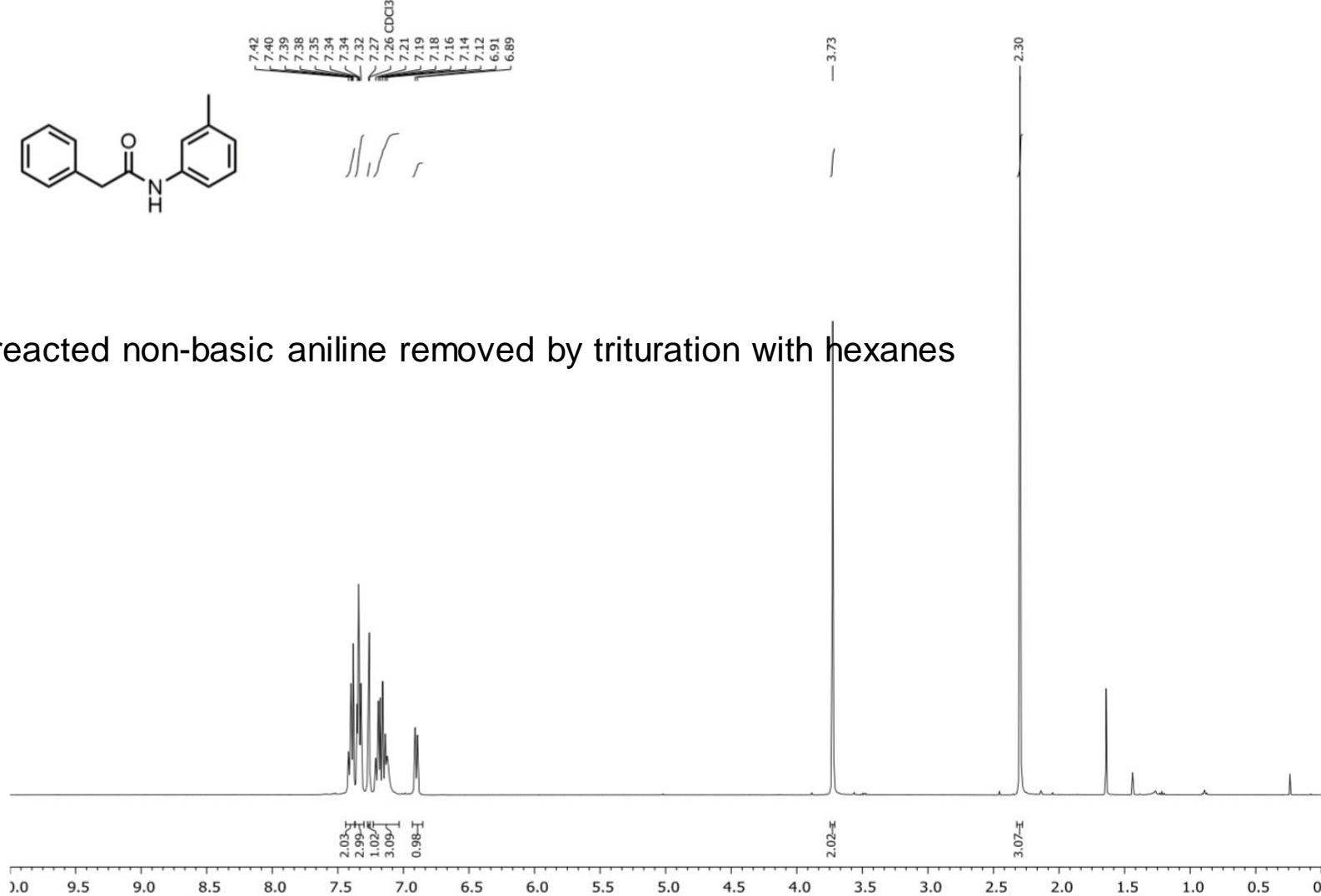
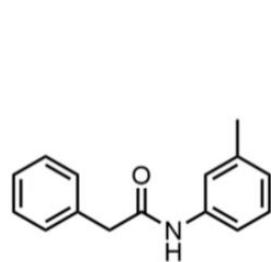
'Crude' Products are Pure!



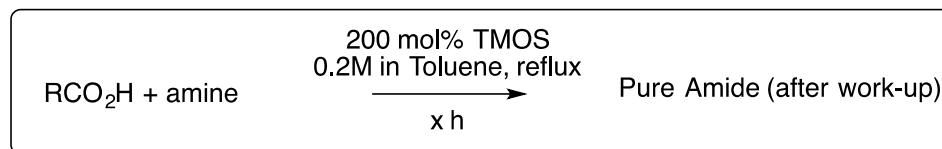
‘Crude’ Products are Pure!



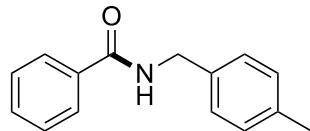
‘Crude’ Products are Pure!



Direct Amidations of Aromatic Carboxylic Acids with TMOS

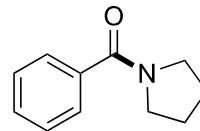


Aromatic acid + primary amines
'Class: Al-1°'

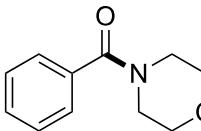


98%
(6h)

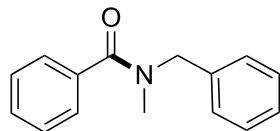
Aromatic acid + cyclic secondary amines
'Class: Al-c2°'



98%
(7h) 96%
(17h)



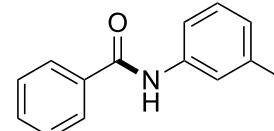
Aromatic acid + acyclic secondary amine
'Class: Al-a2°'



53% conversion
(24h)

250 mol% TMOS, 2M

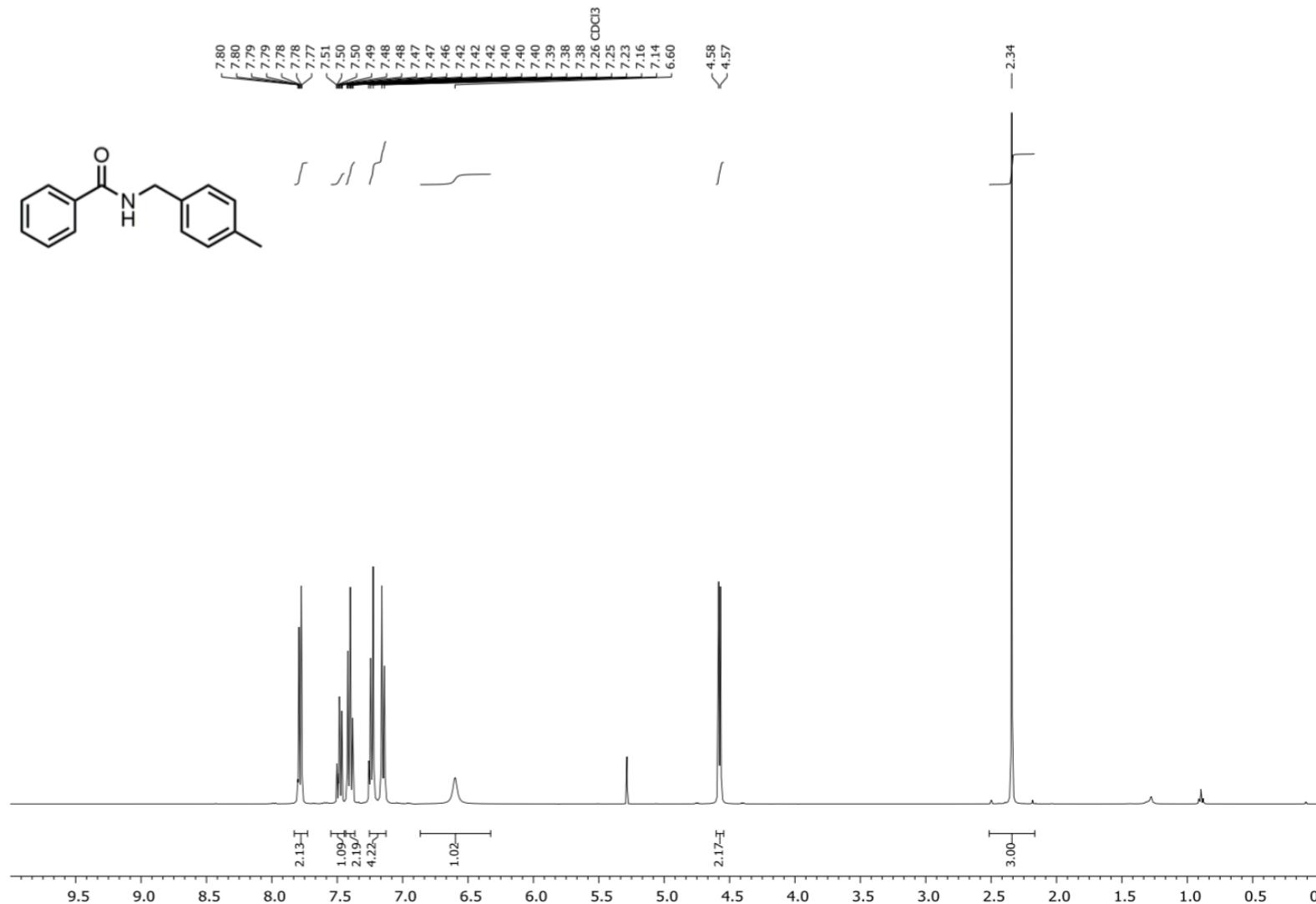
Aromatic acid + aniline
'Class: Al-An'



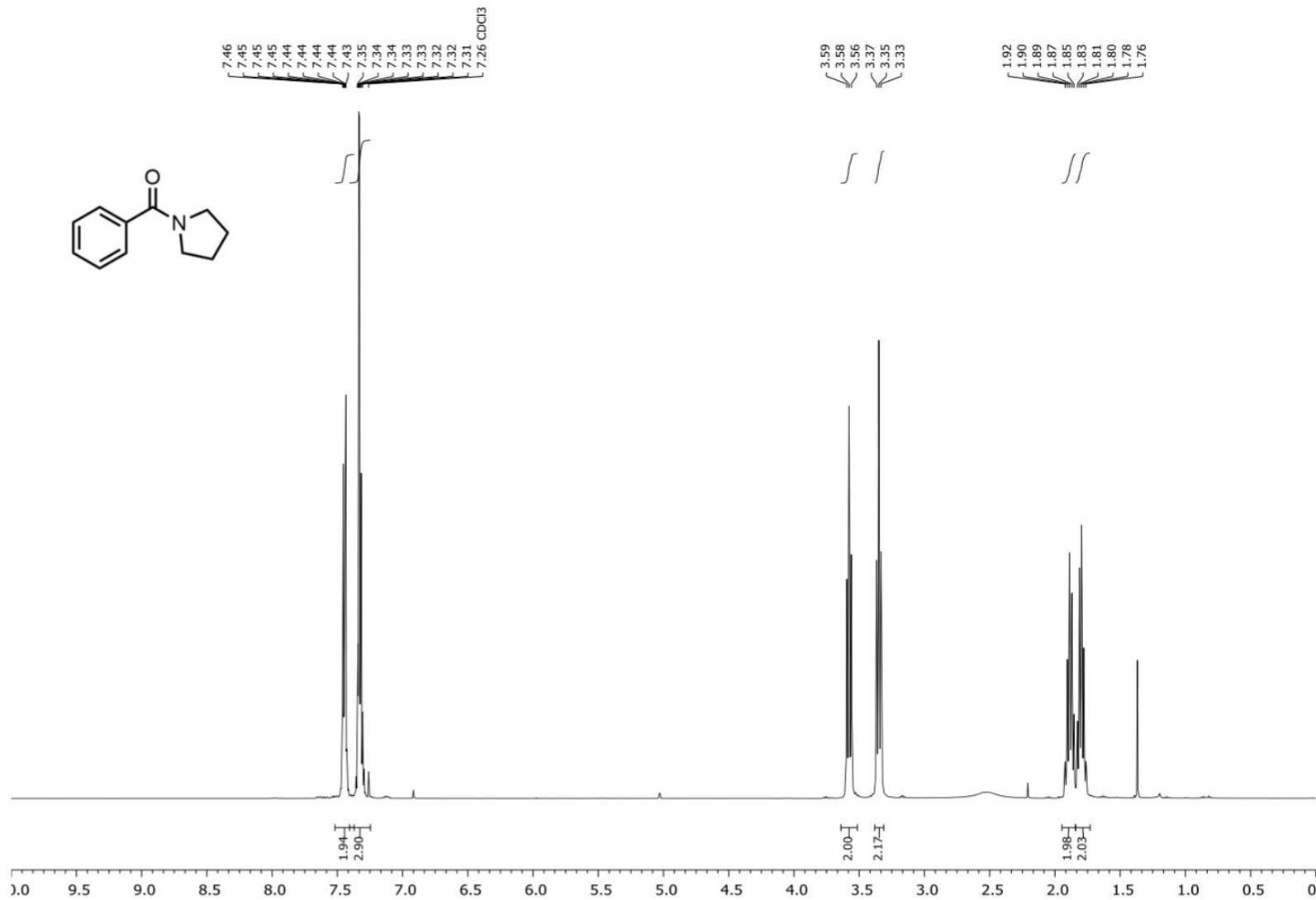
46% conversion
(24h)

250 mol% TMOS, 2M

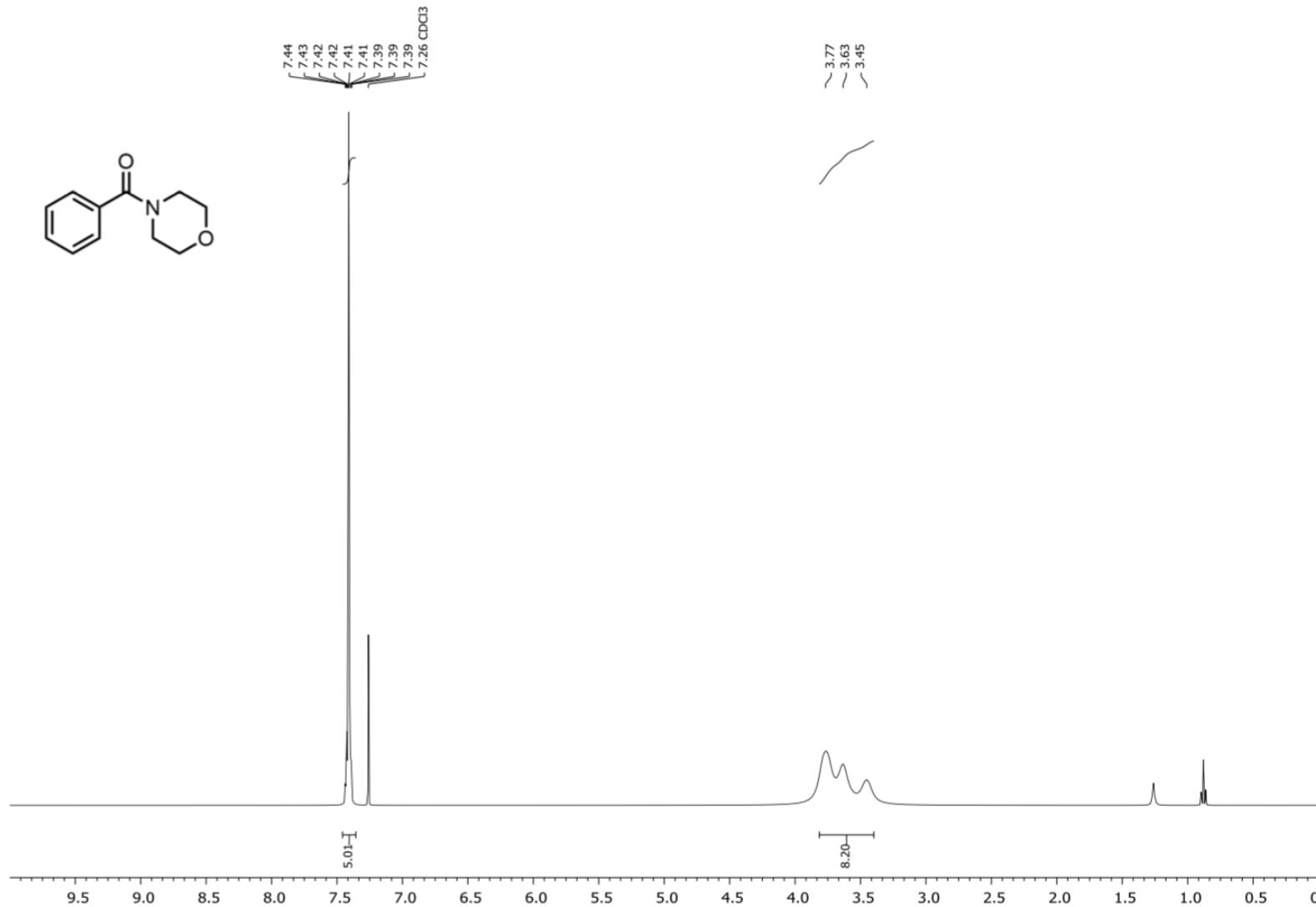
‘Crude’ Products are Pure!



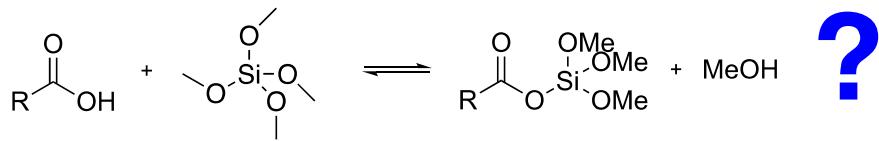
‘Crude’ Products are Pure!



‘Crude’ Products are Pure!

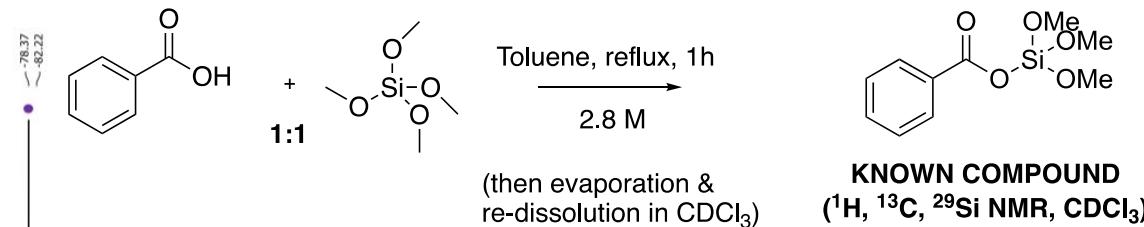


Silyl Ester as *de facto* Activated Species?



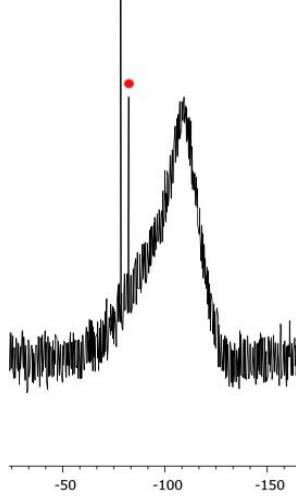
?

- Identification of activated ester?
- Position of equilibrium?



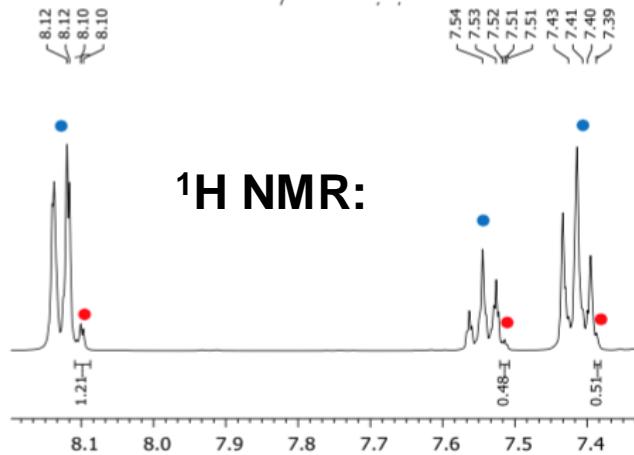
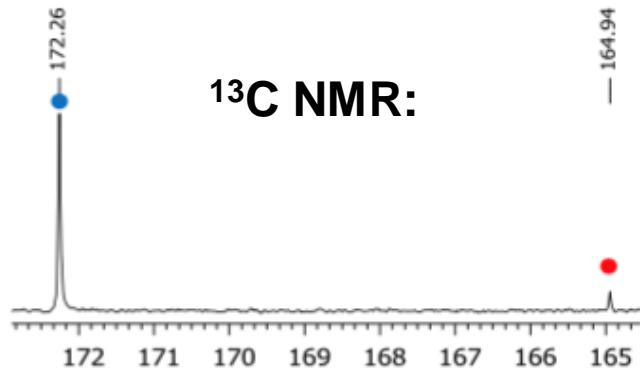
✓ OBSERVED

^{29}Si NMR:



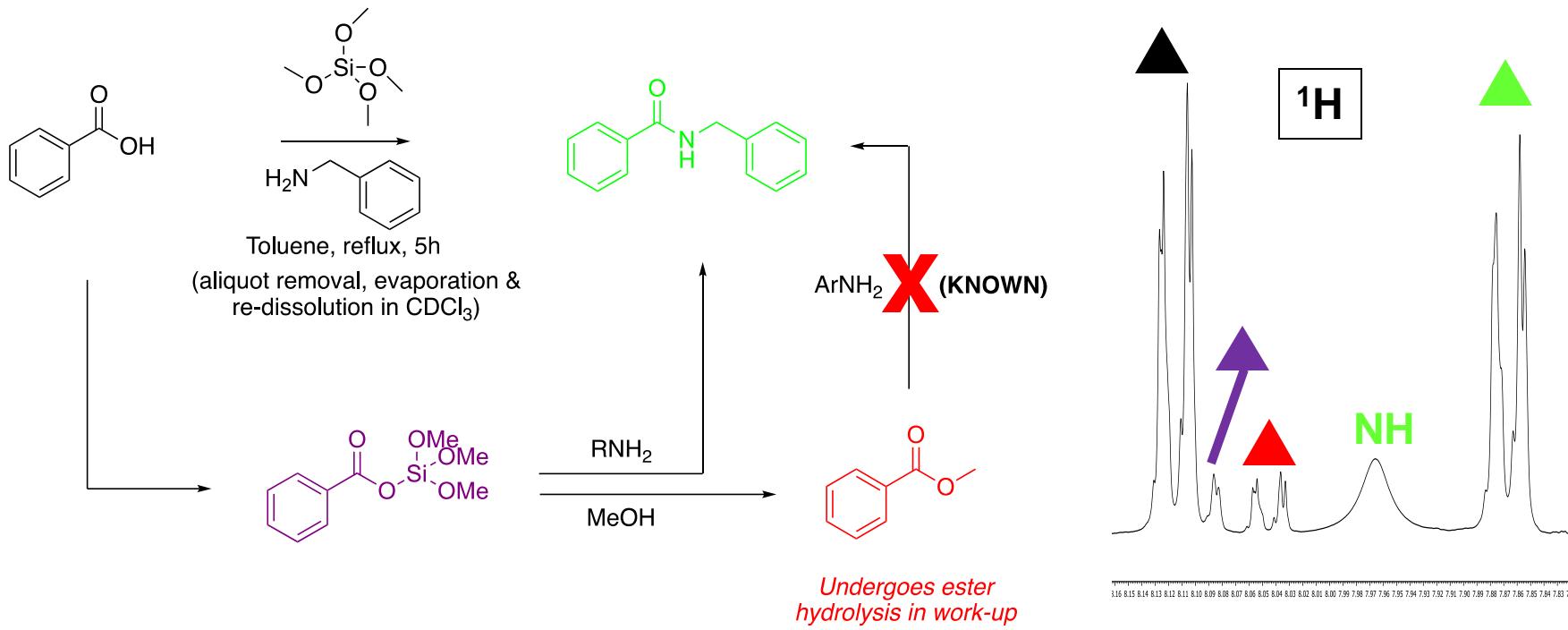
Equilibrium position established as ca. 9:1

^{13}C NMR:



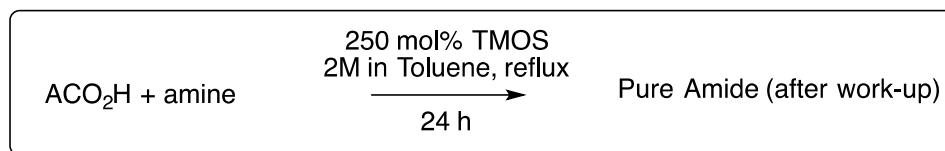
^1H NMR:

Observation under Reaction Conditions?

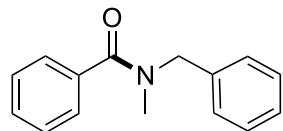


Methanol removal will be beneficial to position of equilibrium & to prevent methyl ester formation when amine nucleophilicity is low

Challenging Amidations Revisited

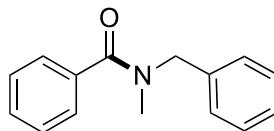


Aromatic acid + acyclic secondary amine
'Class: Al-a2°'



53% conversion

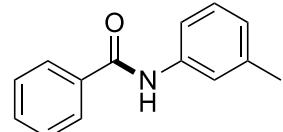
Aromatic acid + acyclic secondary amine
'Class: Al-a2°'



84%
(4Å MS)

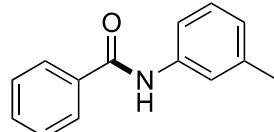
The first quantitative direct amidation of an aromatic carboxylic acid with an aniline

Aromatic acid + aniline
'Class: Al-An'



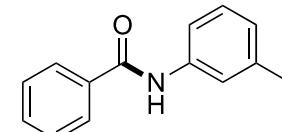
46% conversion

Aromatic acid + aniline
'Class: Al-An'



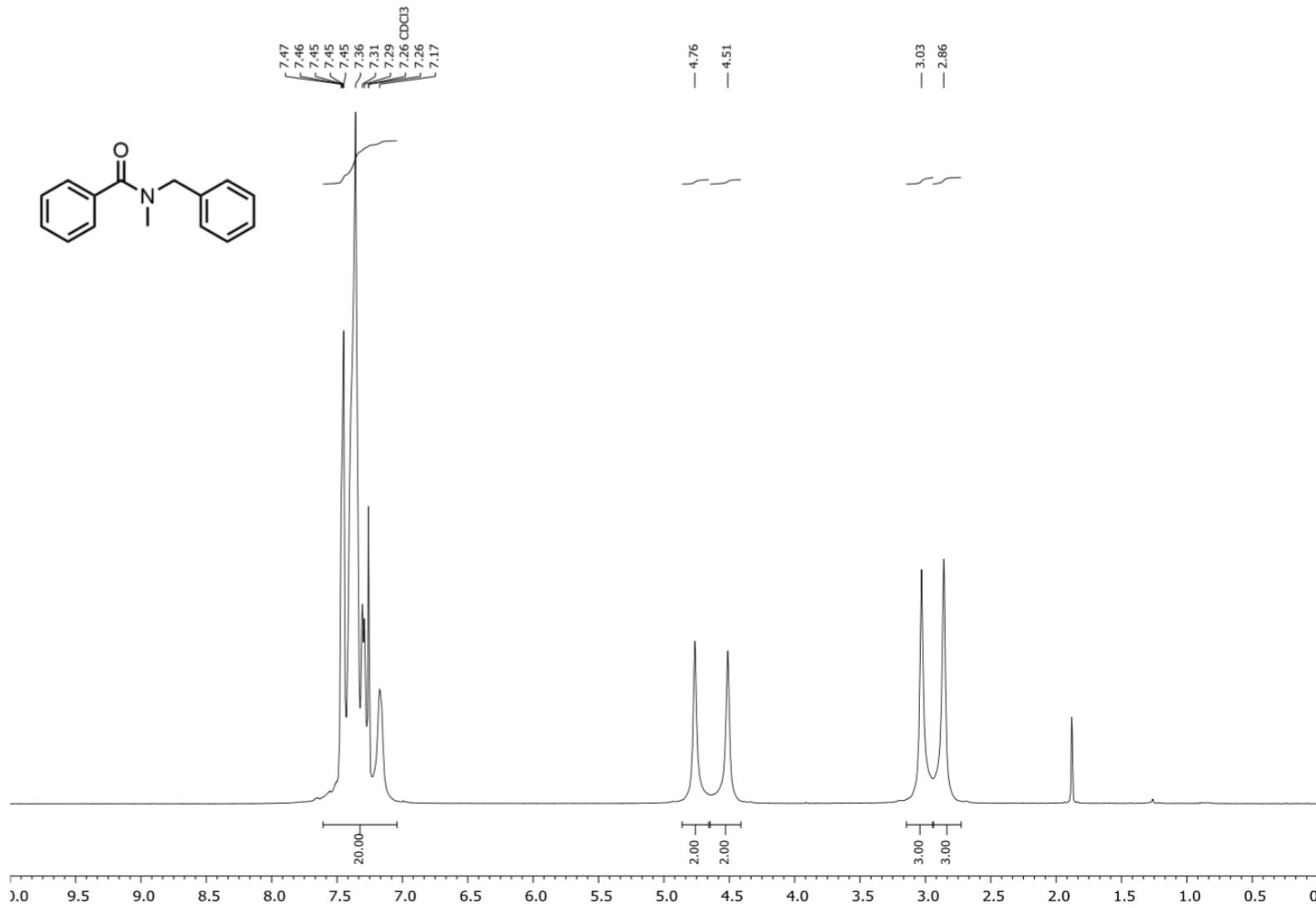
75%
(4Å MS)

Aromatic acid + aniline
'Class: Al-An'

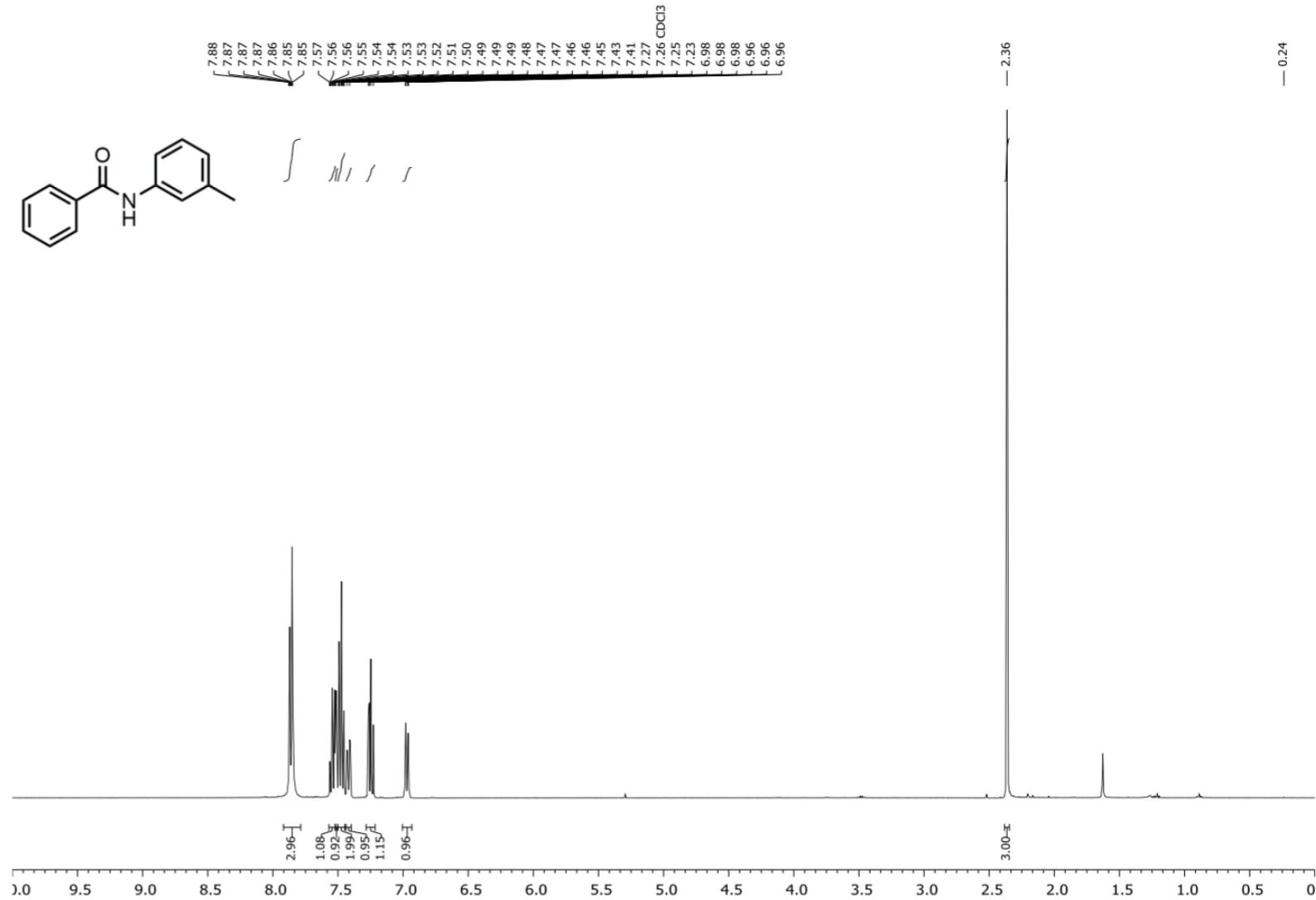


Quant.
(4Å MS +
2 eq. ArCO₂H)

‘Crude’ Products are Pure!

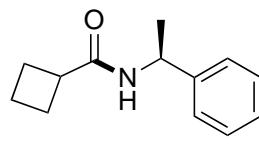
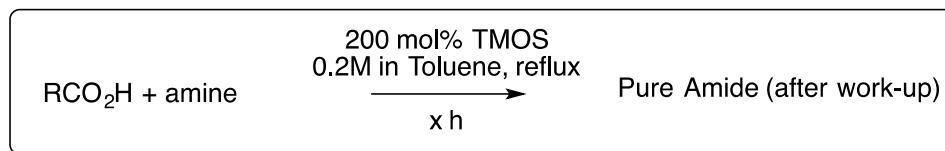


‘Crude’ Products are Pure!

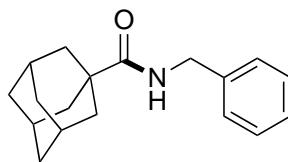




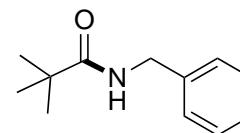
Challenging Direct Amidations



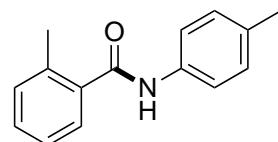
100%
(2h)



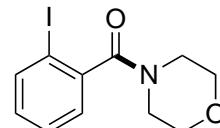
90%
(24h)



99%
(20h)

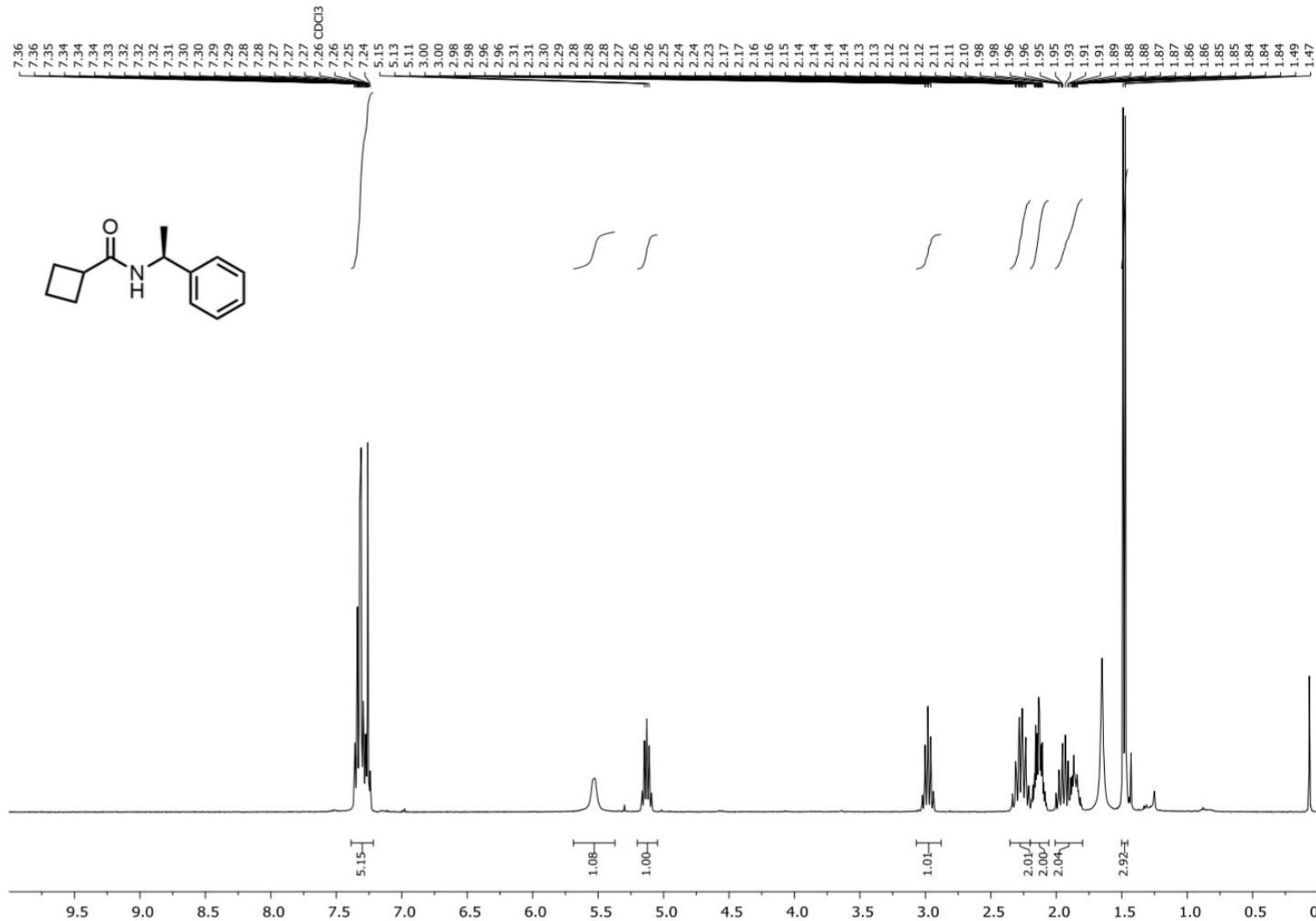


78%
(48h)
250 mol% TMOS, 2M,
(2 eq. Acid)

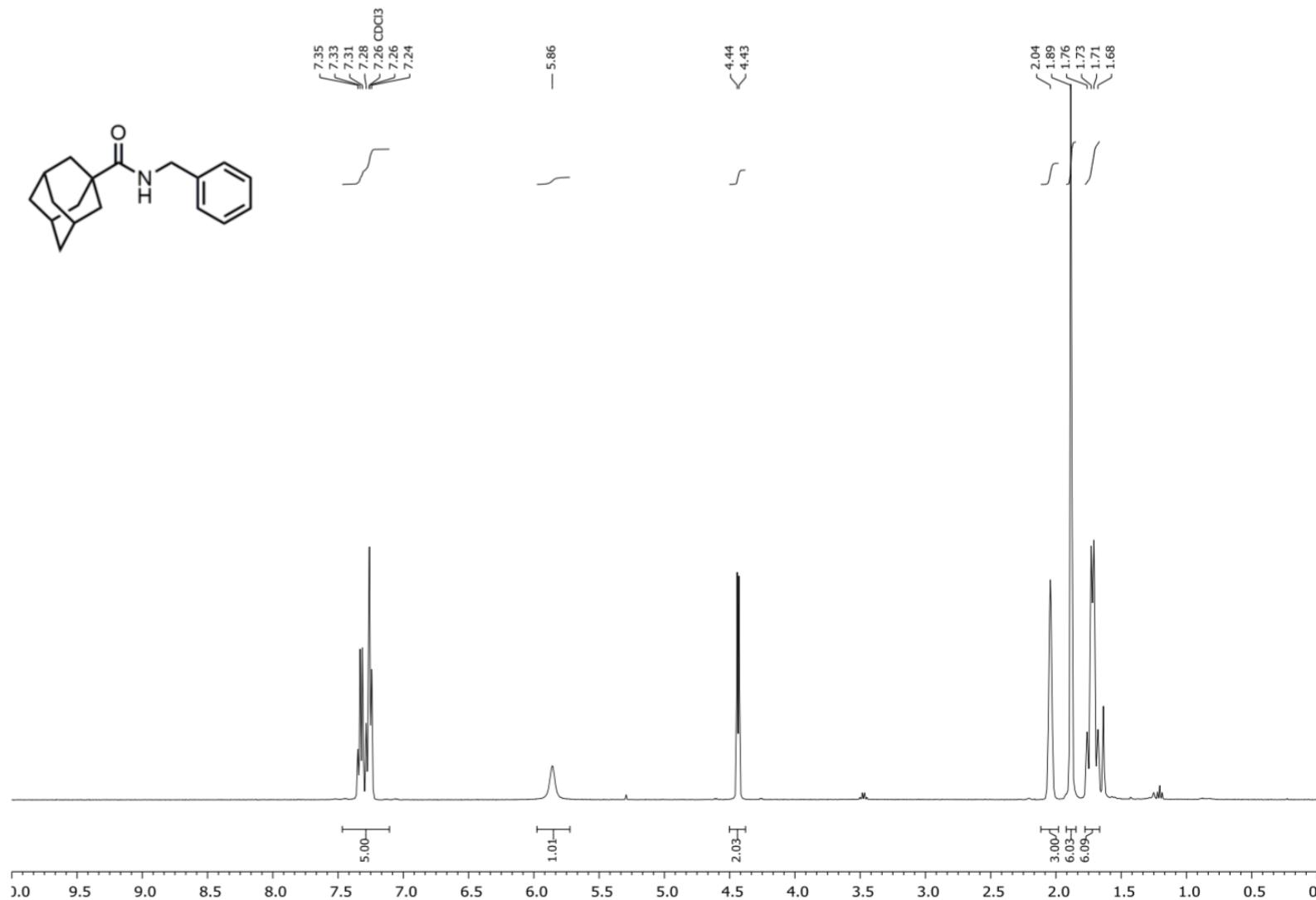


87%
(66h)

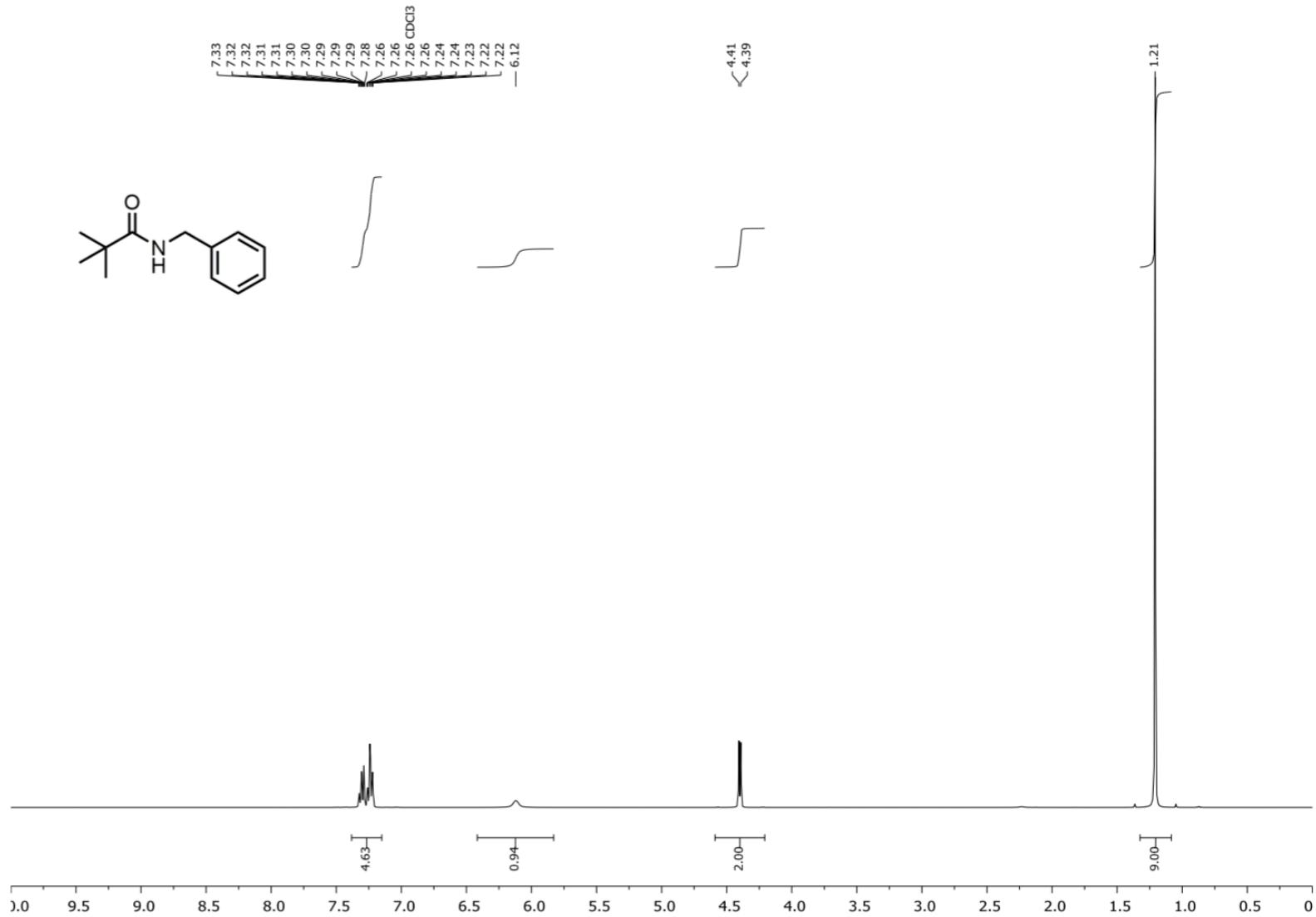
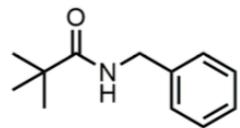
'Crude' Products are Pure!



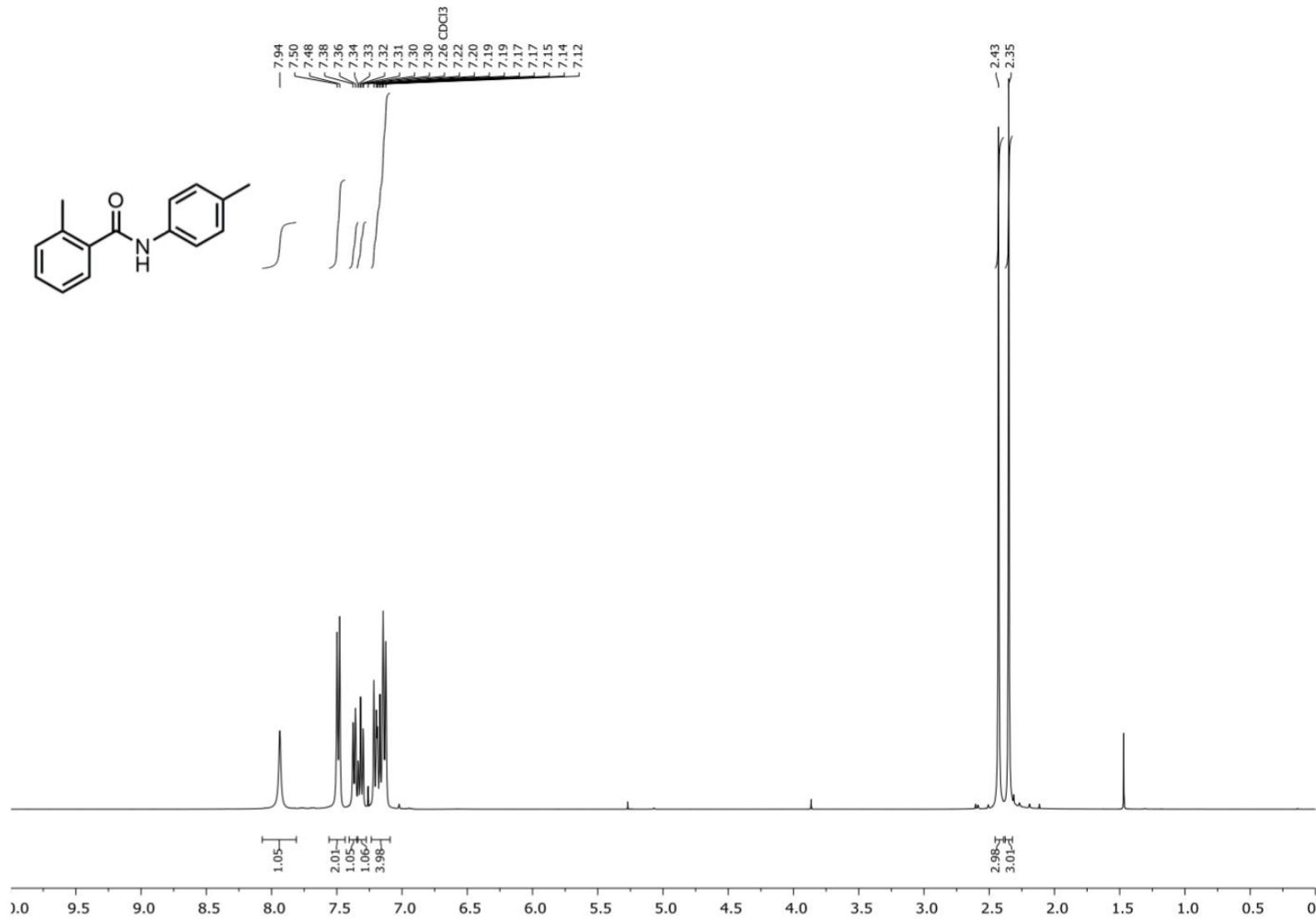
‘Crude’ Products are Pure!



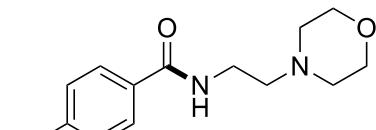
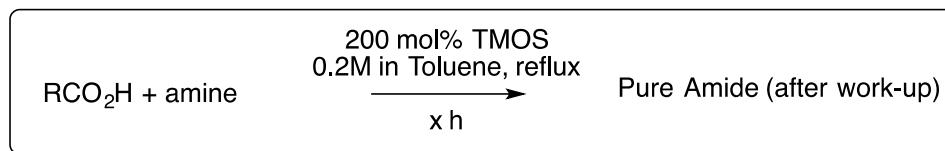
‘Crude’ Products are Pure!



‘Crude’ Products are Pure!

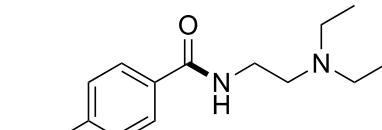


Medicinally Relevant Direct Amidations



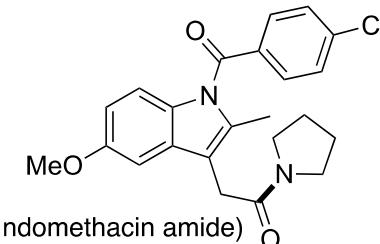
(Moclobemide)
(Anti-depressant)

100%
(1h)



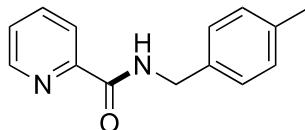
(Procainamide pre-cursor)
(Antiarrhythmic agent)

99%
(3h)

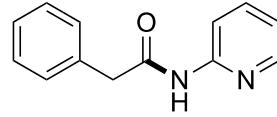


(Indomethacin amide)
(Anti-inflammatory)

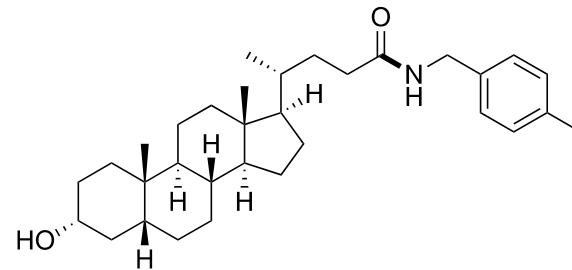
86%
(5h)



84%
(2h)

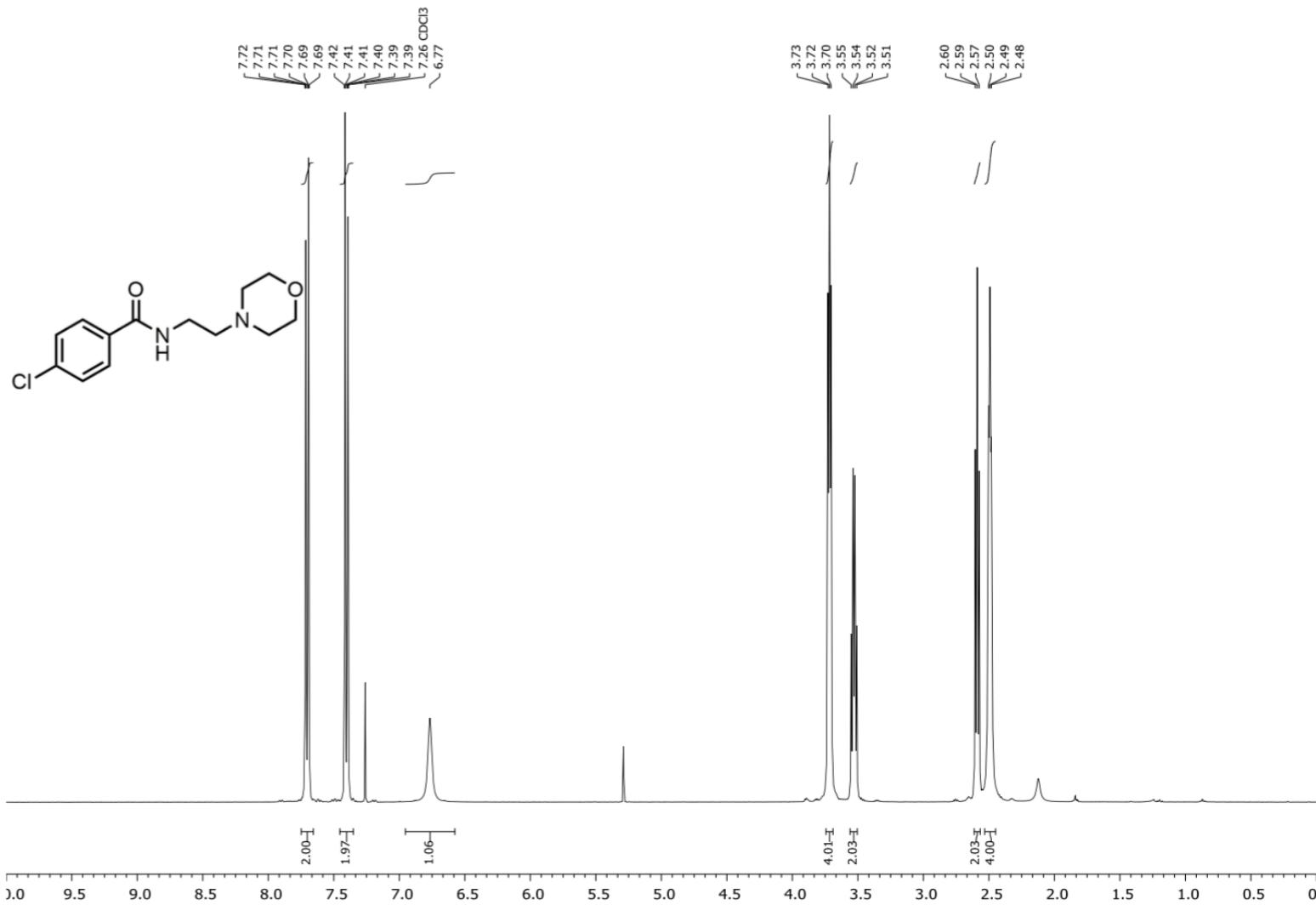


53%
(16h)

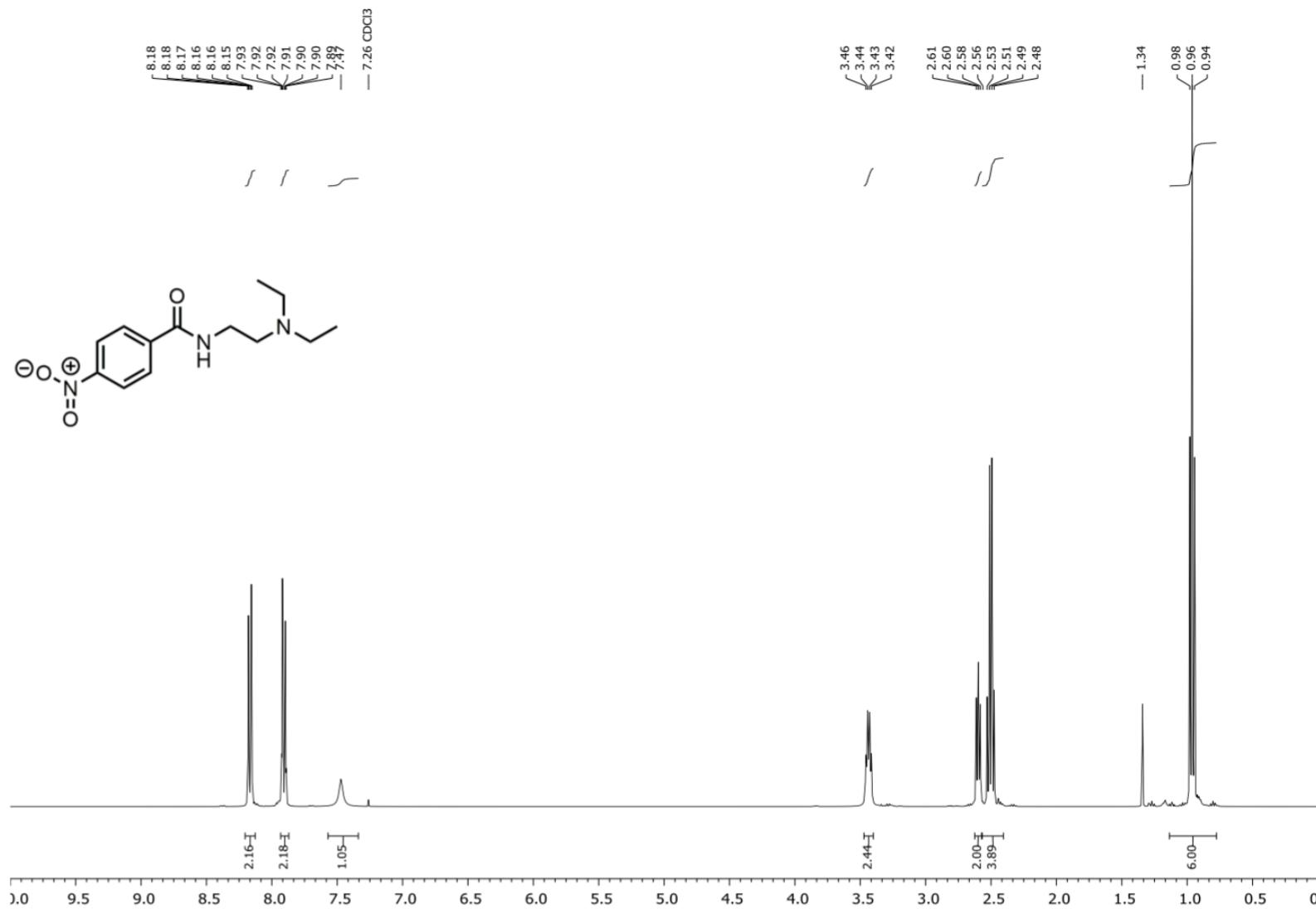


93%
(5h)

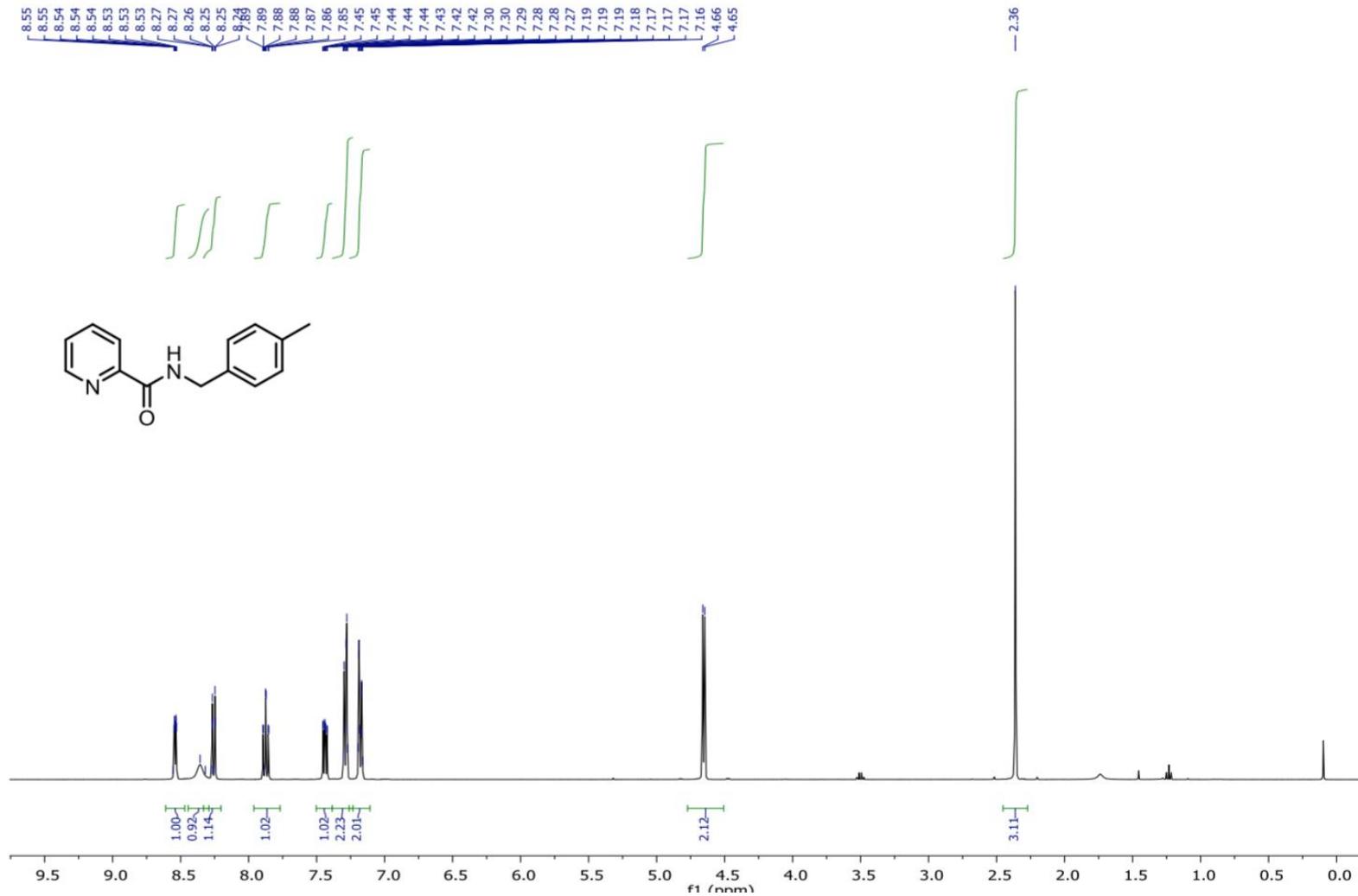
‘Crude’ Products are Pure!



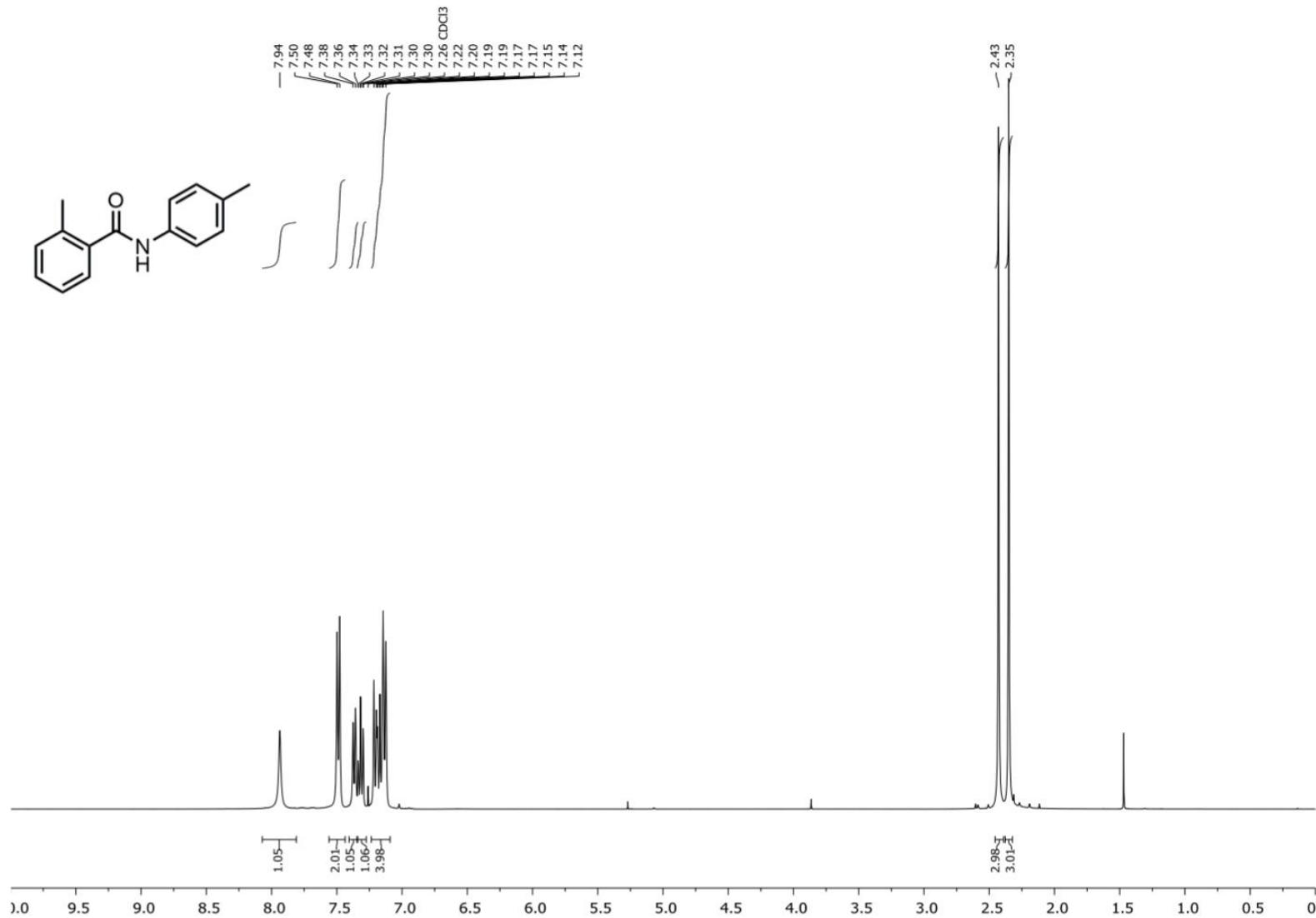
'Crude' Products are Pure!



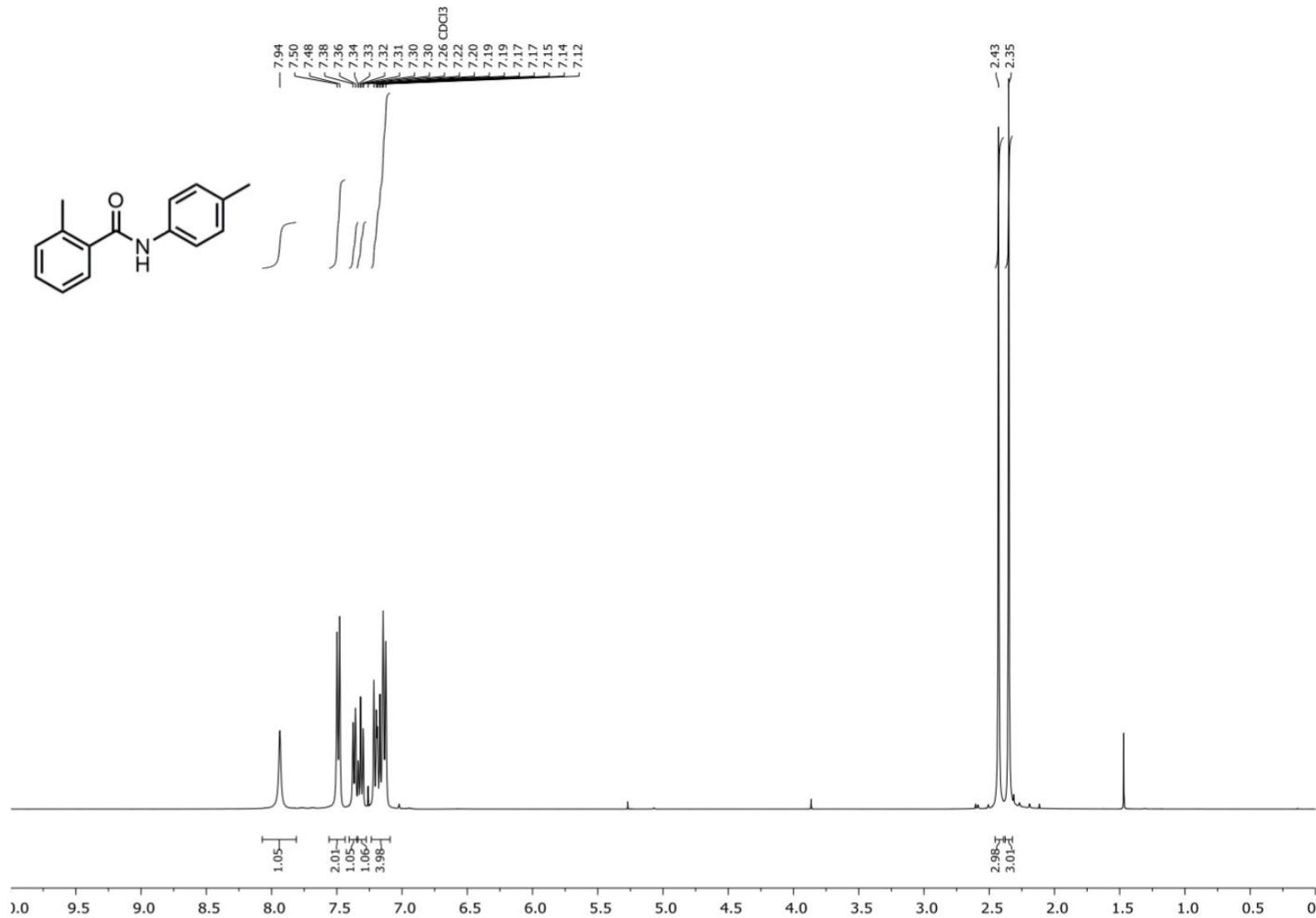
‘Crude’ Products are Pure!



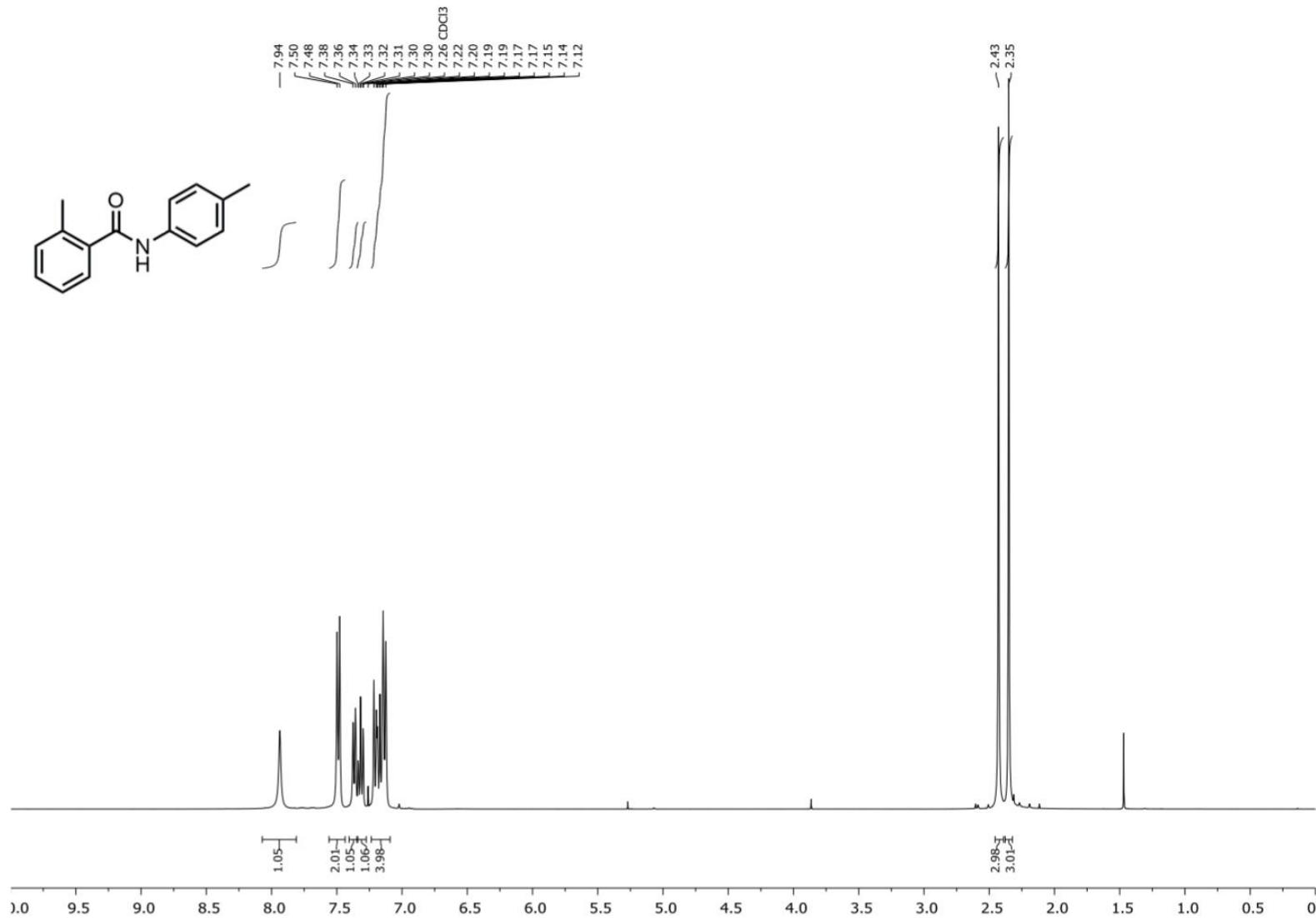
‘Crude’ Products are Pure!



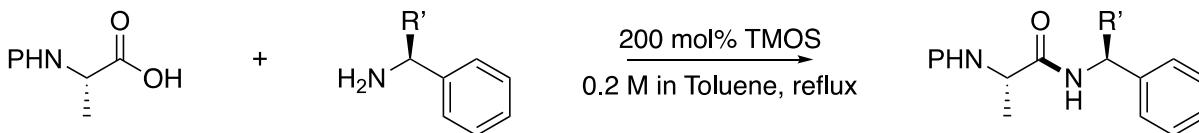
‘Crude’ Products are Pure!



‘Crude’ Products are Pure!

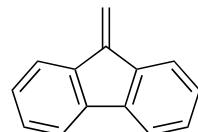
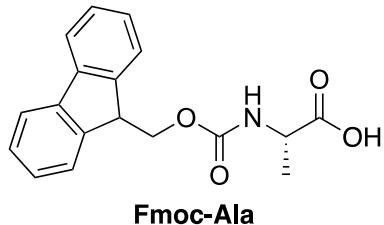


Direct Amidations of Protected Amino Acids



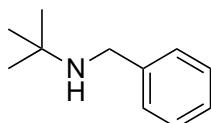
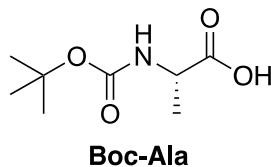
- Protecting group stability?
- Epimerisation?

X



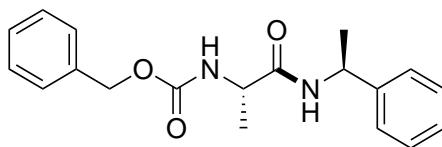
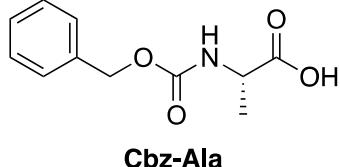
Fmoc deprotection

X



t-Bu transfer

✓



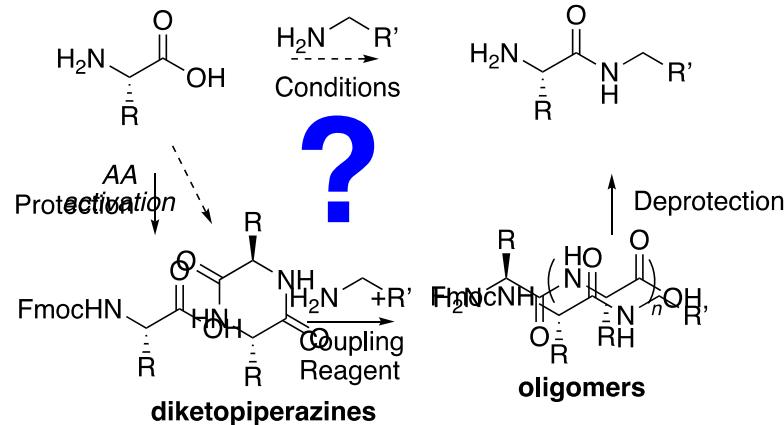
87%
(1.5h)

No epimerization is observed under the reaction conditions

Direct Amidations of Unprotected Amino Acids

Solubility of
zwitterionic
amino acid?

Opportunity to
employ green
solvent?



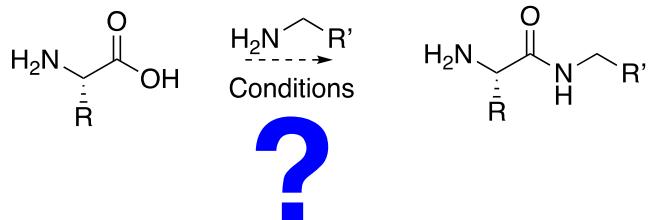
Stereochemical
Integrity?

Chemoslectivity?

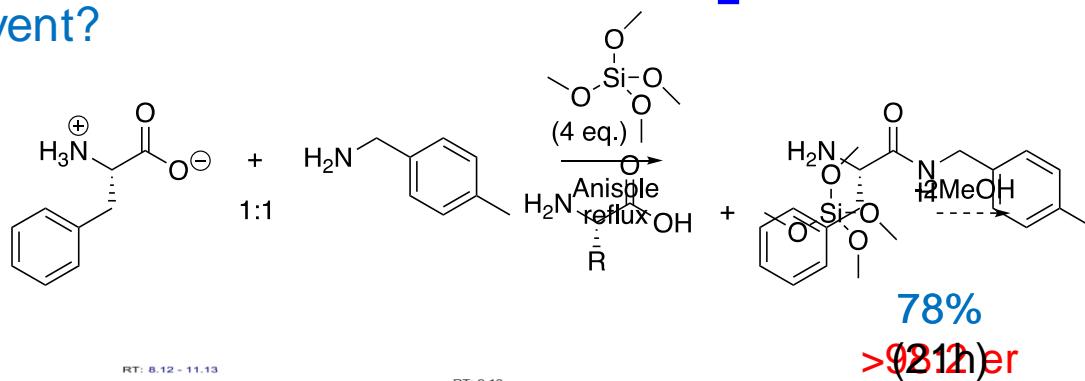
Direct Amidations of Unprotected Amino Acids

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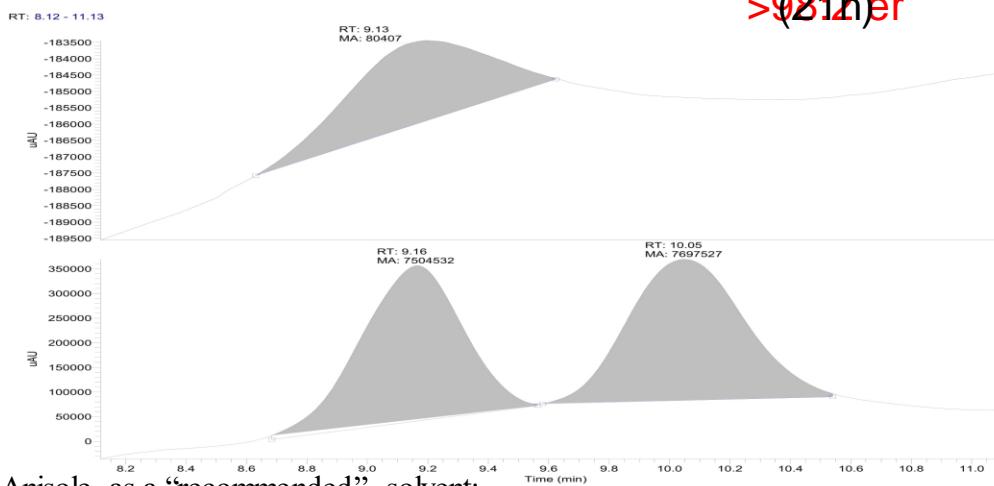
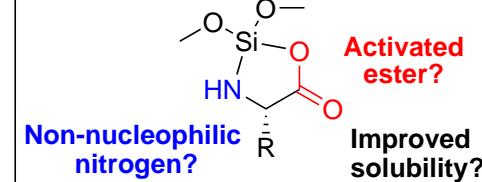
Opportunity to
employ green
solvent?



Stereochemical
Integrity?



Chemoslectivity?

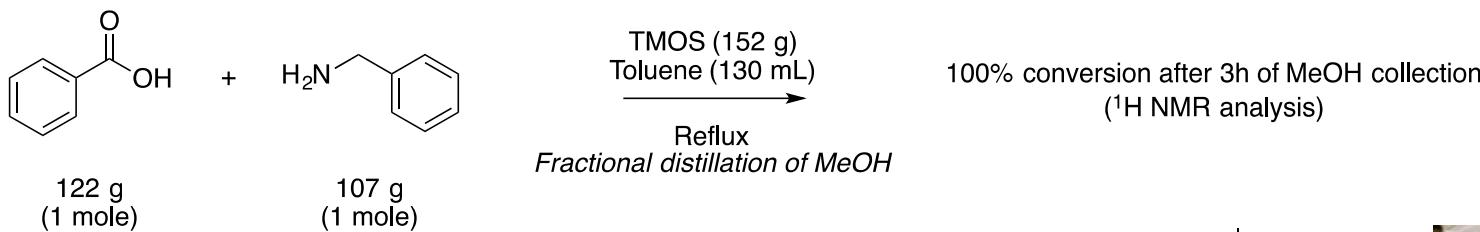


RT:
NL:
UV:
MS:

From L-phenylalanine

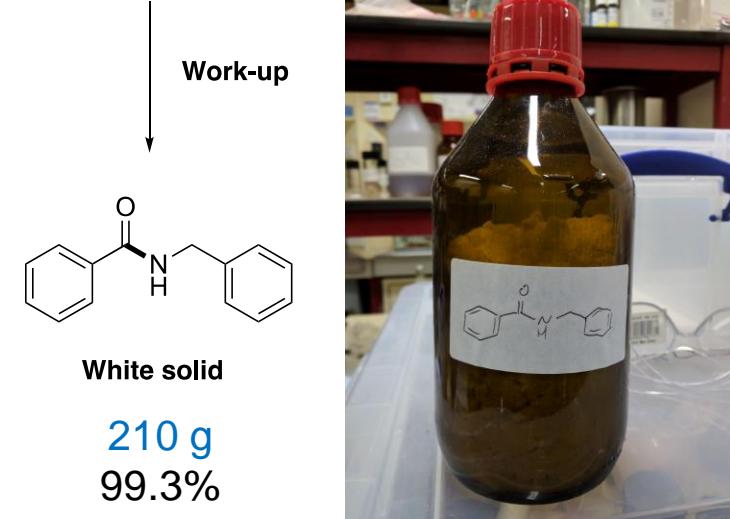
From DL-phenylalanine

Large Scale (1 Mole) Amidation



Work-up:

1. Dilute with THF (1L);
2. Add aqueous K_2CO_3 (0.73M, 1L);
3. Stir 2h (Xs TMOS converted to silica);
4. Filter;
5. Add sat. aq. brine solution (100 mL) - causes phase separation;
6. Separate layers and evaporate organics;
7. Redissolve in CH_2Cl_2 (500 mL);
8. Wash with water (500 mL);
9. Separate, extract aqueous with CH_2Cl_2 (2 x 50 mL);
10. Combined organics, dried over MgSO_4 (20 g), filtered and evaporated.



Process Mass Intensity (PMI): 20

500 mL bottle

[c.f., via acid chloride (PMI: 292) vs HATU (PMI: 178) vs boric acid catalysis (PMI: 89)]

See: Fennie, M. W.; J. M. Roth, J. M. *J. Chem. Educ.* **2016**, 93, 1788–1793.

Acknowledgements

**The Pharmacat
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Engineering and Physical Sciences
Research Council

The Pfizer logo, featuring the word "Pfizer" in a blue, stylized, italicized font inside a blue oval.

Dr Steve Fussell

**TMOS as a Reagent
for Direct Amidation**



Dr David Pugh

Large Scale Amidations



Dr Gajan Santhakumar

**Challenging &
Medicinally Relevant
Amidations**



Ms Shijia Zhu

**Amidations of Unprotected
Amino Acids**

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(EPSRC Arrow/AZ
CASE award)

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Ethers:**

Karl Bonney
(EPSRC DTA)
Mohammad Yaqoob
(EPSRC PDRA)

**Bromoallene epoxidation &
Marilzabicycloallenes:**

James Clarke
(EPSRC DTG)

(and
obtusallenes
synthesis)

**Bicyclic Medium ring ethers:**

Dan-Tiberiu
Sbircea
(MSci project)

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oxides:** Areeb Mahtey**Rearrangements of
Bromoallene oxides:**
Dan O'Reilly**Halomon:**

Alex Jones (EPSRC DTA/
GSK CASE award)

Mariko Whyte &
Alison Gao

Catalytic asymmetric bromolactonisations

Tim Barrett &
Anna Monta



**Bromophycolides
and prenyl RCM:**
Karim Bahou
(CSIRO/IC award)

**Direct Amidations:**

Ben Rowley

Ed Moore (MSci project)
Dyotropic rearrangement

