Amidation

The amide bond is a ubiquitous functionality; occurring in natural products, polymers and pharmaceutical molecules. In publications by Carey *et al.*[1] and Roughley *et al.*[2] investigating the most commonly used chemical transformations in industrial Research and Development (R&D) departments (process and medicinal chemistry) at three large pharmaceutical companies, both included amide bond formation as one of the top ten transformations in these fields. It is therefore unsurprising that amide bonds feature in more than 25% of known pharmaceutical molecules. The top selling drug in 2008 atorvastatin (trade name Lipitor®) with sales of $12.4 billion contains a single amide bond. Other important drug molecules that carry an amide bond include penicillin (antibiotic), paracetamol (analgesic) and chloramphenicol (broad-spectrum antibiotic), Figure 1.

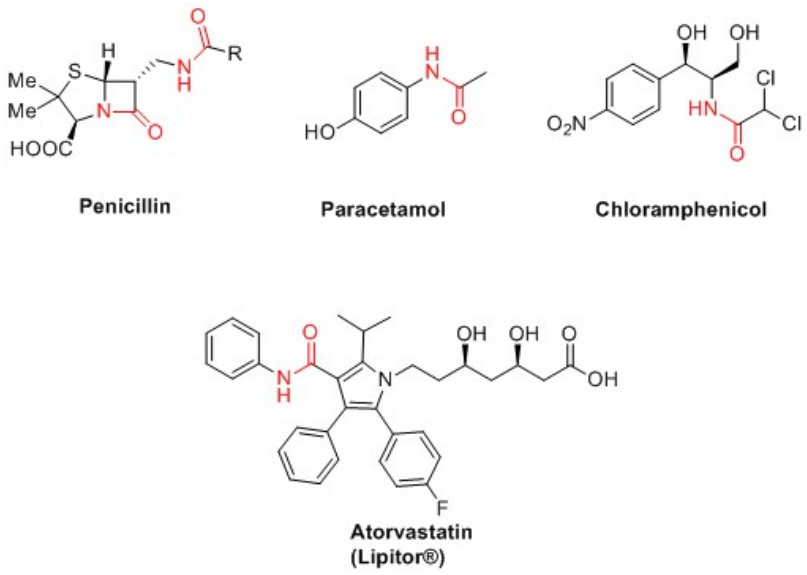

Figure 1: ***Examples of drug molecules carrying an amide bond functionality***

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1. J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, Analysis of the reactions used for the preparation of drug candidate molecules, *Org. Biomol. Chem.*, 2006, 4, 2337-2347.
2. S. D. Roughley and A. M. Jordan, The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates, *J. Med. Chem.*, 2011, **54**, 3451-3479.

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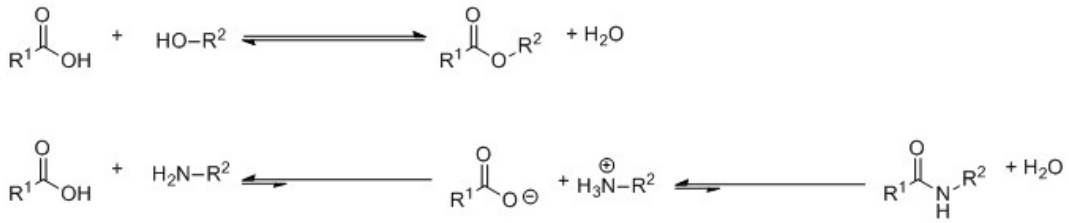
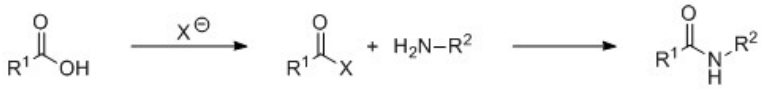
Condensation

Amide bond formation between an acid and an amine are formally condensations. The related esterification reactions are governed by equilibrium however, the mixing of an amine with a carboxylic acid or an acid base reaction forms a stable salt. This means that amide bond formation between these reactants is thermodynamically disfavoured as the equilibrium lies on the side of hydrolysis rather than bond formation, Scheme 1.



Scheme 1: ***Amide bond formation by reaction of an amine with a carboxylic acid is thermodynamically disfavoured***

The subsequent condensation of the salt to give the amide bond can be achieved at high reaction temperatures ~160-180 °C, which is not only energy demanding but can be incompatible in the presence of other functionalities. These forcing reaction conditions have been circumvented by activating the carboxylic acid by using a good leaving group bound to the acyl group of the acid, allowing the necessary attack by the amine group, Scheme 2.



Scheme 2: ***Amide bond formation through activating of the acyl carbon***

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Synthetic methods

Given the importance of amide bonds there is a plethora of synthetic methods and strategies available for their synthesis. The most popular industrial methods for amide bond formation rely on the aforementioned acylation method which account for 16% of all reactions carried out by the pharmaceutical industry, a breakdown of these methods is shown in Table 1.[1]

Table 1: Breakdown of acylation methods for amide bond formation in the pharmaceutical industry [1]

Method	Frequency (%)
Acid Chloride	52
Coupling reagent	21
Mixed carbonic anhydrides	11
Carbonyl Diimidazole	9
Other	6

The use of acid chlorides is the most common method for amide bond formation in industry, and in the majority of cases, the procedure involves *in situ* generation of the acid chloride. Mixed carbonic anhydrides provide a cheap and readily scaled method for *N*-acylation.[1] In recent years the use of carbonyl diimidazole (CDI) has grown in popularity, as it is moderately priced and also readily scaled and worked up, however its use is limited as CDI is a sensitiser and its use on large scale is costly.[1] The use of acyl chlorides and mixed anhydrides is an economical approach to the synthesis of amides, however all of these acylation methods use stoichiometric quantities of coupling agents, which make them expensive, wasteful and inefficient.

Amide bond formation using enzymatic catalysis circumvents the poor atom economy associated with coupling agents, as well as the potential hazards related with the use of

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non-aqueous media chemical approaches. Methods such as lipase-catalysed amidation of carboxylic acids and the hydrolysis of nitriles catalysed by nitrile hydrolases are clean, efficient and safe routes to the synthesis of primary amides. Equally, the use of peptidases and acylases circumvents the need for protection/deprotection steps, which has a positive impact on the mass intensity of the process. The use of enzyme catalysed amide bond formation has the advantage of operating under mild reaction conditions and their specificity leads to excellent regio- and stereoselectivity. Despite the progress made in the area of biocatalytic amide bond formation and some commercial success, enzyme catalysed amide synthesis still suffers from a narrow substrate specificity and material intensive isolation stages, which limit their application.[2]

1. J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, Analysis of the reactions used for the preparation of drug candidate molecules, *Org. Biomol. Chem.*, 2006, 4, 2337-2347.
2. D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. Johnnie L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, Key green chemistry research areas-a perspective from pharmaceutical manufacturers, *Green Chem.*, 2007, **9**, 411-420.

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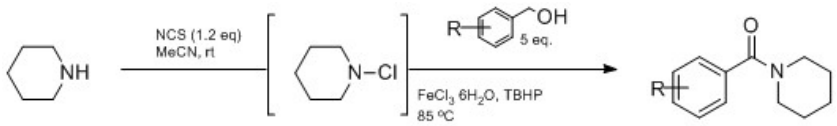
Case studies

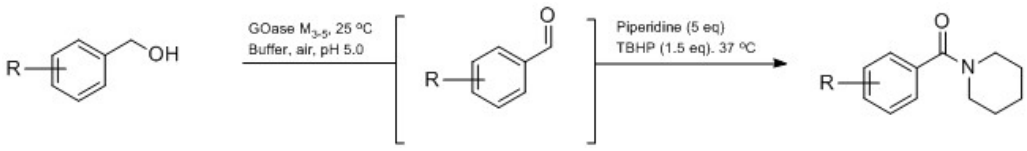
There has been an increased interest in the development of catalytic oxidative amidation reactions to form amide bonds through the coupling of aldehydes to amines. The reactions are thought to proceed *via* oxidation of the resultant imine or hemi-aminal intermediates and are catalysed by transition metals such the platinum group metals, base metals such as iron and copper,[1][2][3][4][5][6][7] lanthanides as well as organo-catalysts.[8][9] These are normally associated with stoichiometric terminal oxidants such as *tert*-butyl hydroperoxide (TBHP), hydrogen peroxide or oxone.

It is possible to achieve the product amide from the alcohol derivative (usually used in large excess), which would undergo oxidation to the aldehyde *in situ* as shown in **Scheme 1**.[10] Coupling methods from the aldehyde starting material give good to excellent yields however, aliphatic and heteroaryl aldehydes are known to give a lower yield and as such require higher reaction temperatures. Therefore, the development of a catalytic methodology for the formation of amides from such starting materials without the need for stoichiometric chlorinating agents or a large excess in aldehyde could offer an attractive alternative.



Scheme 1: ***Iron catalysed tandem reaction for the formation of amides from benzylic alcohols (De Luca et al., 2013 [10])***

CHEM21 researchers have developed a one-pot tandem reaction for the Bio-Chemo catalytic conversion of benzylic alcohols to aldehydes in the first step, with subsequent reaction with an amine in the presence of TBHP to give the product tertiary amide. The reaction proceeds at mild temperatures (25-37 ˚C), and proceeds as a one-pot, two-step process (**Scheme 2**).[11]



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Scheme 2: ***Catalytic Bio-Chemo Cascade for the formation of amides (Turner et al. 2014[11])***

The system tolerates a wide range of benzylic alcohols containing electron deficient aromatic rings, with 4-nitrobenzene exhibiting the highest yield in product amide at 91%. This bio-chemo cascade offers mild reaction conditions, material efficiency and circumvents the need for air and moisture exclusion. Although method the shown in **Scheme 1** is an excellent example of where the synthetic community is beginning to move away from the use of catalysts based on precious metals and making use of the more earth abundant metals such as iron, one could argue on closer scrutiny of the both approaches, that there is little difference between them. However, we chose such an example to highlight the energy and material savings that can be made when biocatalysts are considered over chemocatalysts.

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3. J. Wei Wei Chang and P. Wai Hong Chan, Highly Efficient Ruthenium(II) Porphyrin Catalyzed Amidation of Aldehydes, *Angew. Chem. Int. Ed.*, 2008, **47**, 1138-1140.
4. S. Muthaiah, S. Chandra Ghosh, J. - E. Jee, C. Chen, J. Zhang and S. Hyeok Hong, Direct Amide Synthesis from Either Alcohols or Aldehydes with Amines: Activity of Ru(II) Hydride and Ru(0) Complexes, *J. Org. Chem.*, 2010, **75**, 3002-3006.
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9. J. W. Bode and S. S. Sohn, N-Heterocyclic Carbene-Catalyzed Redox Amidations of α-Functionalized Aldehydes with Amines, *J. Am. Chem. Soc.*, 2007, **129**, 13798-13799.
10. S. Gaspa, A. Porcheddu and L. De Luca, Iron-catalysed oxidative amidation of alcohols with amines, *Org. Biomol. Chem.*, 2013, **11**, 3803-3807.
11. B. Bechi, S. Herter, C. McKenna Shane and Riley, S. Leimkühler, N. J. Turner and A. J. Carnell, Catalytic bio–chemo and bio–bio tandem oxidation reactions for amide and carboxylic acid synthesis, *Green Chem.*, 2014, **16**, 4524–4529.

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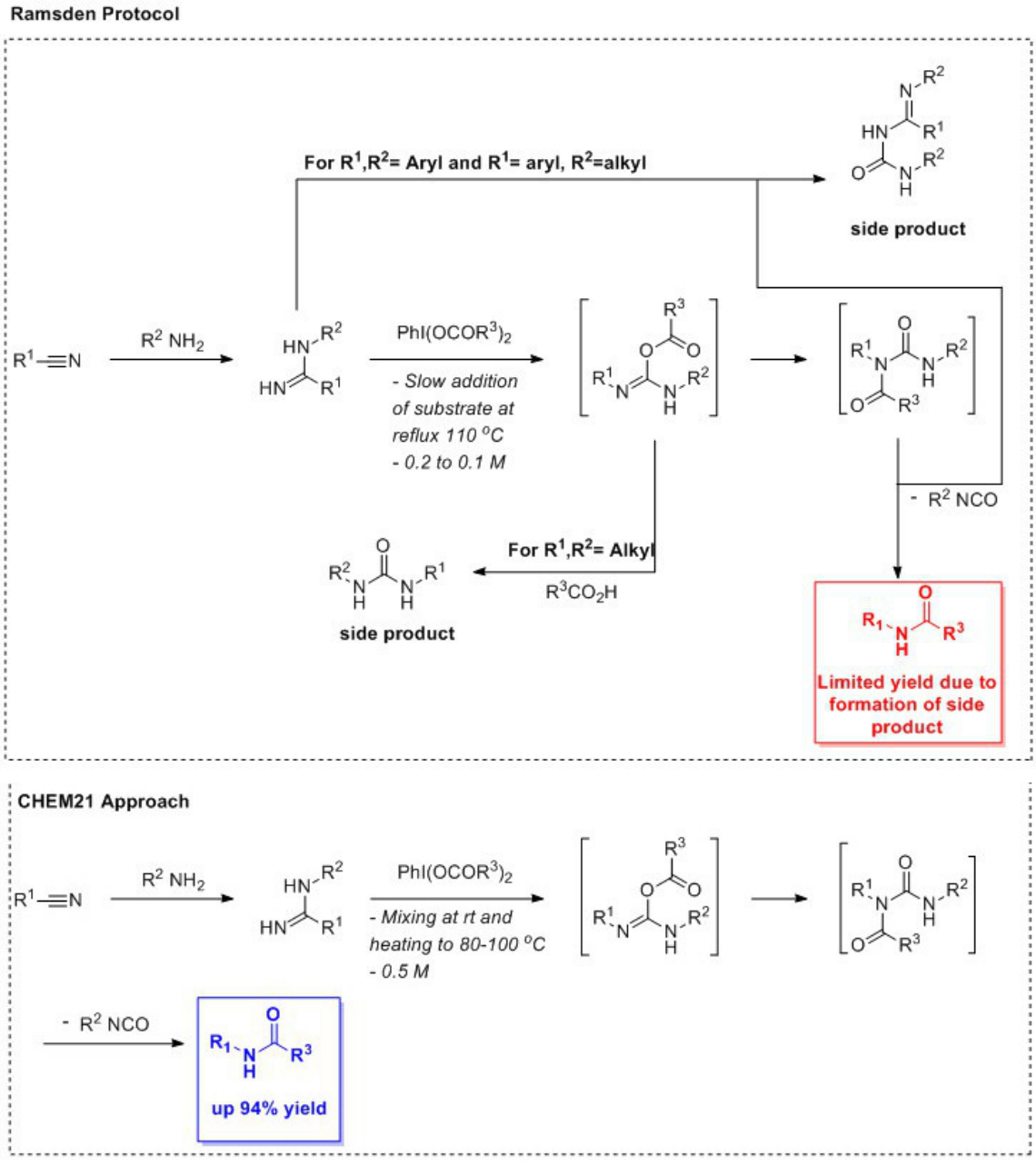
Case study 2

There is a huge interest in the development of efficient synthesis of secondary amides that involve the construction of C(sp^2)-N bond. In the late 1990's, Ramsden *et al*. [1][2][3] described a phenyliodine(III) diacetate (PIDA)-mediated oxidative rearrangement of *N*-substituted amidines, however they found that the reaction product is dictated by the nature of the substituents on the amidine (**Scheme 1**).[4]



Scheme 1: ***Ramsden and CHEM21 approaches to the synthesis of secondary amides***

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from aliphatic and aromatic nitriles [4] [5]

Building on these preliminary results by Ramsden, the CHEM21 researchers investigated whether Ramsden's protocol could be optimised to allow the efficient, direct and high yielding rearrangement of *N*-substituted amidines to their corresponding secondary amides without side product formation. This was achieved by modifying the manner in which the experiment was executed. By using other hypervalent iodine reagents than PIDA, other secondary acetamides were also accessible. *N*-Substituted amidine substrates are accessible from nitriles through the Pinner reaction or by direct activation with Lewis acids;[5] and as such reagents are commercially available, this approach provides a general and simple access route to amides from nitriles and hypervalent iodine reagents.[4]

Through this research the CHEM21 researchers developed an efficient tandem oxidative rearrangement-elimination reaction that allows access to secondary amines, especially those based on hindered carboxylic acids, or bulky/electron deficient amines that cannot be obtained efficiently from condensation reactions.[4]

1. C. A. Ramsden and H. L. Rose, Oxidative rearrangement and cyclisation of N-substituted amidines using iodine(III) reagents and the influence of leaving group on mode of reaction, *J. Chem. Soc., Perkin Trans. 1* , 1997, 2319-2328.
2. M. Bobosikova, W. Clegg, S. J. Coles, M. Dandarova, M. B. Hursthouse, T. Kiss, A. Krutosikova, T. Liptaj, N. 'a Pronayova and C. A. Ramsden, The oxidative rearrangement of furan-2-carboximidamides: preparation and properties of 2-acylaminofurans, *J. Chem. Soc., Perkin Trans. 1* , 2001, 680-689.
3. C. A. Ramsden and H. L. Rose, Rearrangement and cyclo-[small alpha]-elimination of N-substituted amidines using (diacetoxyiodo)benzene, *J. Chem. Soc., Perkin Trans. 1*, 1995, 615-617.
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5. T. R. M. Rauws and B. U. W. Maes, Transition metal-catalyzed N-arylations of amidines and guanidines, *Chem. Soc. Rev.*, 2012, **41**, 2463-2497.

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Summary and further reading

In their survey of the reactions used by the pharmaceutical industry in the production of drug candidates, Carey *et al.*[1] note that not a single catalytic method was used for the synthesis of amides. There is still a pressing need for scalable catalytic methodologies for the synthesis of amides that are atom efficient and avoid the production of waste; this has encouraged research into the efficient preparation of amide bonds.

Recommended reading

- F. K. Ferdousi and A. Whiting, Green Catalytic Direct Amide Bond Formation, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016, ch. 13, pp. 156-164.

Details on recent developments in the synthesis of amide bonds can be found in the following reviews:

- E. Valeur and M. Bradley, Amide bond formation: beyond the myth of coupling reagents, *Chem. Soc. Rev.*, 2009, **38**, 606-631.
- C. A. G. N. Montalbetti and V. Falque, Amide bond formation and peptide coupling, *Tetrahedron*, 2005, **61**, 10827-10852.
- V. R. Pattabiraman and J. W. Bode, Rethinking amide bond synthesis, *Nature*, 2011, **480**, 471-479.

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