The Isocyanide S_N2 Reaction

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Abstract

The nucleophilic substitution reaction (S_N2) is one of the oldest, yet very useful organic transformations and has found widespread applications for the synthesis of drugs and natural products. Typically, cyanide, oxygen, nitrogen, sulfur, or phosphorous nucleophiles replace a halogen or sulfonyl ester leaving group to form a new bond between the nucleophile and the electrophile. Isocyanides display an unusual versatile chemistry based on their C-centered lone pair s and the C-centered p^* frontier orbitals leading to radical, and multicomponent reactions. Surprisingly, the nucleophilic character of isocyanides has never been explored in S_N2 reactions. We discovered that isocyanides react as versatile nucleophiles in S_N2 reactions with alkyl halides in a general manner to afford highly substituted secondary amides by *in situ* hydrolysis of the intermediate nitrilium ion. The innovative 3-component reaction has a broad scope regarding the structures of the isocyanide and electrophile components, functional group compatibility, scalability, use for late-stage modification of a drug and synthesis of highly complex compounds otherwise not easily accessible from simple precursors. The chemical space of the new reaction is not only different but nearly doubled in size compared to the classical amid coupling. Significantly, the isocyanide nucleophile comprises an unusual Umpolung amide carbanion synthon R-NHC(-)=O, useful as an alternative to the classical amide coupling.

Introduction

The amide bond is one of the most common functional and structural elements, as the backbones of all natural peptides and proteins and almost every second drug are composed of amide bonds. Thus, construction of amide bonds is fundamental to organic synthesis as it provides access to the backbone of pharmaceuticals, agrochemicals, natural products, peptides and proteins and functional materials (Fig.1A). Recent data mining charting the amine–acid cross-coupling space revealed that there are numerous opportunities for reaction discovery.[1] Nonetheless, the great majority of amide groups are formed by coupling of the an nucleophilic amine and an electrophilic carboxylic acid building block. Notably, the direct coupling of amines and carboxylic acid is unfavorable, hence requires an activated esters which is formed by aggressive, expensive or waste-full reagents (Fig.1B).[2] Far less common ways to form amides involve for example oxidative and radical-based methods or the alkylation of nitriles to yield nitrilium ions with *in situ* hydrolysis.[3-4] Based on our longstanding interest in isocyanide chemistry we asked ourselves to which degree the known boundaries of isocyanide nucleophilicity can be pushed to exploit new and synthetically useful reactivities. The isocyanide has both, a s-type *C*-centered HOMO and a *C*-centered p-type LUMO which accounts for the unusual reactivity of isocyanides.[5] An example for this is its ability to act both as a nucleophile and an electrophile in the a-addition of a nucleophile and an electrophile onto the same functional group atom, the isocyanide-*C*, which is a quite unusual feature in organic chemistry, and accounts for many reactions of isocyanides such as multicomponent reactions and heterocycle syntheses.[6-8] Due to their unusual *C*-only centered reactivity, isocyanides were also coined ‘stereochemical chameleons’.[9]

Isocyanides in multicomponent reaction chemistry (IMCR) is probably the most famous application. It involves the nucleophilic attack to the electrophilic oxo and imine-*C* and the subsequent addition of an internal or external nucleophile onto the nitrilium-*C*, followed by a rearrangement and is well established in the Passerini and Ugi reactions.[7, 10] Motivated by the powerful IMCR which is based on the unusual reactivity of the isocyanide-*C* we designed a novel multicomponent reaction (Fig.1C). Our design involves an initial nucleophilic attack of the isocyanide on an alkyl halide in the sense of a nucleophilic substitution reaction (S_N2); the intermediate nitrilium ion then reacts with water to give the stable amide species. Conceptually and experimentally the reaction design is not obvious and potential issues preventing the planned reaction outcome could involve i.a. insufficient isocyanide nucleophilicity, premature hydrolysis of the isocyanide or the alkyl halide.

Results

Reaction optimizations

The S_N2 reaction is known to be very sensitive to the substrate structures, as well as reaction conditions.[11-13] While initial attempts to run the new reaction were promising by masspectrometry analysis, the yields were far from being synthetically useful. Taking into account the established condition knowledge of the S_N2 reaction we first interrogated stoichiometry and ratio of the reactants, temperature, temperature source, and solvents employing high throughput experimentation (HTE).[14-15] HTE methods used were parallel reactions in 96, 48, and 24-well format, parallel heating in a metal block, parallel TLC analytics, and stacked injection into SFC. The methods are described in more detail in the SI. We chose the model reaction of p-chloro benzyl isocyanide with benzyl bromide, a good electrophile in S_N2 reactions and good visibility of educts and product in TLC (Fig.2). Next, we investigated the result of additives in the S_N2 reactions. Biphasic phase transfer catalyst (PTC) were often used in S_N2 reactions to increase yields and conversion.[16] We screened 16 different common PTCs (SI). The addition of iodine salts is often described as advantageous in the S_N2 reactions as it converts the less reactive chloride leaving groups into the more reactive iodo leaving group. After thorough optimization of all parameters the optimized conditions involved the microwave heating at 105^oC for 3 h of 1:2 ratio of isocyanide, alkyl halide, 20 mol% KI catalyst, and 1 equivalent of water in acetonitrile in the presence of 2 equivalent of the inorganic base K_2CO_3 (Fig.2).

Scope and limitations

The substrate scope for this reaction is very broad (Fig. 3-5). With the optimized conditions in hand, we interrogated the scope of the halide with respect to the leaving group, sterical bulkiness, electronic nature and diversity. Amongst the halide leaving group, chloride, bromide and iodide reacted well according to the well-established leaving group trend I>Br>Cl. To test the functional group tolerance, we successfully reacted 21 different alkyl halides with adamantyl isocyanide on a mmol scale (Fig.3). Adamantyl isocyanide is a solid, non-smelling, bench stable powder which has been synthesized recently on a mol

scale.[17] A variety of alkyl halides with different functionalities were well tolerated. The small methyl group can be easily introduced (**21a**), whereas bulky alkyl groups or alkyl groups with b-branching do not react. Long chain alky groups can be introduced (**17a**), also with a terminal phthalic amide amine protecting group (**12a**), whereas Boc-protecting groups were found to be not stable under the microwave conditions (SI). For several alkylation products, single crystals revealed X-ray structures which support the structural identity (**4a, 8a, 12a, 16a**). Allyl (**5a**), and benzyl (**1a, 3a, 4a, 6a, 13a**) groups react well due to the conjugated nature of the pentagonal bipyramidal transition state as suggested by the classical S_N2 literature. Specifically, to mention is bis benzylchloride derived **13a** which can be mono alkylated in 32% yield, and can be potentially further reacted through the unreacted benzylchloride. Also, the nature of the heterocyclic structures which could be reacted is quite diverse, including benzimidazole (**7a**), pyrazole (**8a**), triazole (**9a**), phthalimide (**12a**), coumarin (**11a**), thiophene (**15a**), and quinoline (**19a**). Especially to mention are **15a** and **18a**, which are formed from bifunctional (hetero)aromatic benzylchloride benzaldehydes. The aldehyde functionality can be further derivatized as will be shown below. We also found substrates which did not give the expected products or gave very low yields (<30%, SI).

The evaluation of the isocyanides also revealed a broad scope (Fig.4). We reacted 20 different isocyanides with methyl iodide in satisfactory to good yields. Benzylic (**23a**, **24a**, **25a**, **29a**, **30a**), aromatic (**31a**, **33a**, **34a**, **35a**, **36a**, **37a**), aliphatic (**27a**, **42a**) and heteroaromatic (**26a**, **28a**, **32a**) isocyanides all worked well. When isocyanides with a basic side chain were reacted, we observed the double alkylation and a quaternary amine salt formation (**38a**, **39a**). Noteworthy, also a-amino acid isocyanides (**40a**, **41a**) worked well.

We performed a number of mixed examples to further elaborate the scope and usefulness of the reaction (Fig.5). Highly substituted **47a** is especially noteworthy, as it comprises a combination of a sterically hindered a,a-disubstituted cyclopropyl benzyl isocyanide with a bifunctional 4-formylbenzyl chloride. The new method is also applicable to the facile synthesis of diverse lipid derivatives (**56a**, **60a**, **61a**) which could be of interest in lipidomics applications. Bulky isocyanides (**47a**, **50a**, **54a**) and phenyl isocyanides with bulky o-substitutents (**43a**, **51a**, **52a**, **53a**, **55a**) reacted nicely. Amide **55a** is accessible with a free compatible benzylic hydroxyl group. 4-Methylpentenoic acid (pyroterebic acid) ester or amides are common in biologically active isoprenoid compounds from plants. Compound **54a** is a pyroterebic acid amide and it comprises an unprecedented synthesis. Another example of incorporation of an isoprenoid side chain (homo geranyl acid) is exemplified in **60a**. It is conceivable that this methodology can be used to incorporate isotope labeled carboxy-*C* via the isocyanide. In summary, complex structures can be accessed from simple available building blocks in one step.

Scaling and late-stage functionalization

To further stress the reaction performance, we evaluated the robustness of this reaction towards pharmaceutical late-stage diversification on an actual drug.[18] Late-stage-functionalization is a drug discovery technique to selectively derivatize already complex ‘drug-like’ molecules and is used to further improve their properties.[18] Phenoxybenzamine (dibenzyline) is an alpha blocker used for the treatment of

hypertension. To establish the usefulness of our novel S_N2 reaction we reacted dibenzyline with adamantyl isocyanide and were able to isolate the expected amide product in 40% yield (Fig.6).

Having demonstrated a robust substrate scope for this novel isocyanide to amide transformation, we considered a variety of applications. First, we performed the thiophene carbaldehyde on a gram scale in fair yields. For this we reacted 1.59 gram of the bifunctional 5-(chloromethyl)thiophene-2-carbaldehyde with 1.61 gram adamantyl isocyanide on a 10 mmol scale (Fig. 6). The product **15a** could be isolated in 51% yield (1.57 gram). We envisioned that the aldehyde group can be further functionalized to create molecule of high complexity in just a few steps. To increase the complexity of the products we used multicomponent reactions (MCR) for further derivatization of the thiophene carbaldehyde.[7, 10, 19] The carbaldehyde **15a** is of interest to test further reactivity due to its unprotected aldehyde group based on the functional group compatibility of the reaction. Thus, we used **15a**, each in a Ugi-4CR, a Groebke Blackburn Bienaymé (GBB-3CR) reaction, and a Ugi tetrazole reaction to exemplify rapid increase of molecular complexity (Fig. 6). The Ugi-4CR product **1b** was obtained in 72% yield in one step from easily available building blocks. Noteworthy, an alkynyl amide is introduced in a straight forward mild manner. Electrophilic alkynyl amides are often used in covalent drug discovery targeting cysteines and an alkynylamide substructure can be found in the FDA approved Acalabrutininb Bruton's tyrosine kinase targeting drug.[20] Next, we investigated aldehyde **15a** as a substrate in the GBB-3CR reaction. The GBB-3CR is a popular method to synthesize highly substituted bicyclic imidazo heterocycles which already have proven their value as drugs and candidates.[21] Thus, we reacted 2-aminopyridine with aldehyde **15a** and cyclohexyl isocyanide in a GBB-3CR, under microwave conditions in methanol to obtain complex heterocycle **1c** in 36% yield. Lastly, we performed a Ugi tetrazol reaction employing aldehyde **15a**. Tetrazoles are often used as advantageous carboxylic acid bioisosteres, and can be broadly obtained by multicomponent reaction chemistry.[19]

In summary, the new S_N2 reaction turned out to be scalable, useful in late-stage-functionalization, and can yield highly interesting intermediates for allowing further chemistries to increase structural diversity in a quasi-exponential complexity increase, in just three steps: isocyanide synthesis, S_N2 reaction, further aldehyde reaction.

Mechanism and chemical space

Preliminary observations support a S_N2-type mechanism (Fig.7A). Accordingly, the nucleophile isocyanide attacks from the backside to form a trigonal bipyramidal transitions state **I** and kicks out the leaving halogen anion. The intermediately formed nitrilium ion **II** undergoes water attack on the isocyanide-C **III**, and through tautomerization reveals the final amide **IV** upon hydrolysis.

Several lines of evidence support a S_N2 mechanism: sterically hindered substrates such as neopentyl iodide or isobutylbromide do not give any reaction product; the reaction is strongly solvent dependent and runs well in the polar solvent DMF which are believed to stabilize the transitions state, but not in apolar toluene or protic methanol; the reaction rate depends on the nature of the nucleofuge as reported in the

S_N2 literature I>Br>Cl (SI). To exclude a possible radical mechanism, we performed the reaction in the presence of 2x stoichiometric amounts of the radical quencher TEMPO, and did not find any difference in the reactivity (SI).[22-23] While running the reaction in the absence of water and direct injection in the mass spectrometer we could observe a strong peak corresponding to the bromo nitrilium ion (Fig.7B). In conclusion, there is strong evidence that the reactions run according to a S_N2 mechanism. In the classical amide coupling approach the carbonyl is a carbocation synthon, while in the S_N2 approach the rare amide carbanion synthon is the result of an Umpolung (Fig.7D). The isocyanide is commonly synthesized from its primary amine precursor (Ugi method: formylation > dehydration or Hoffman reaction).[10, 24] Alternatively, the isocyanide can be produced from an aldehyde or ketone precursor through reductive amidation with formamide (Leukart Wallach) and dehydration (Fig.7C).[25-26] Phenomenologically, the overall transformation of this S_N2 reaction corresponds to a coupling of a primary amine with a C1 synthon derived from chloroform (Hoffmann) or formic acid (Ugi) with an alkyl halide or coupling of an aldehyde/ketone through a NC synthon derived from formamide (Leukart-Wallach) with an alkyl halide (Fig 7.C). Due to the large number of commercially available primary amines and aldehydes and ketones as isocyanide precursors, and alkyl halides, the reaction can be of considerable synthetic utility. Noteworthy, in classical S_N2 reactions mostly very simple nucleophiles are used (such as halides, CN^-, thio- or alcoholates), whereas the herein described S_N2 reaction can make use of the great structural diversity of isocyanides (Fig.4). This is leading to a strong increase in structural complexity upon coupling with alkyl halides (e.g. **60a**). Next, we asked the question whether the new reaction can access a chemical space different from the classical amide coupling. For this we investigated the commercial availability of the corresponding carboxylic acid needed to form the target amides and compared them with the corresponding halide (SI). Surprisingly, in 52% cases the corresponding carboxylic acids were not commercially available at all. Noteworthy, in the remaining 48% the carboxylic acid was on average 2.3 times more expensive than the corresponding chloride. It turned out that the chemical space accessible by the two orthogonal amide syntheses is very different and only 12% are overlapping (i.e. can be synthesized by both methods). In conclusion, our herein reported novel S_N2 reaction is of high synthetic value as it allows to access a chemical space which otherwise can only accessed through time-consuming and lengthy multistep syntheses and leads to a strong increase in molecular complexity, otherwise uncommon in S_N2 reactions.

Discussion

Arguably, the amide bond formation is amongst the most important reactions in organic chemistry. The value of the amide group in organic chemistry cannot be overstated. It is on top of the most frequent functional groups occurring in bioactive molecules described in medicinal chemistry literature.[27] More than 1/2 of the marketed drugs contain at least one amide group. Thus, the amide bond formation is the most practiced reaction in medicinal chemistry and one of the most frequently used in process chemistry.[2] While the classical amide coupling is a powerful reaction, there are many more hypothetical ways in which amides can be formed, with each new transformation imprinting a unique accessibility

fingerprint on the product. Discovery of novel reactivities is key to leverage untapped chemical space and to broaden the tool box used in medicinal and other chemistries,[28] exemplified by a recently described copper-catalyzed deaminative esterification with broad scope.[29] The use of isocyanides in S_N2 reactions is such an example of unprecedented reactivity giving access to unusual otherwise difficult to synthesize amides. Classically the amide group is constructed from a carboxylic acid derivative and a primary or secondary amine using specific activation conditions and a plethora of aggressive, expensive, and waste-full coupling reagents have been described.[2] Therefore, sustainable and alternative amidations have emerged as an important synthetic strategy to exploit the commercial and natural prevalence of the amide functional group,[30-31] leading us to consider the transformation of an isocyanide into an amide by alkylation and hydrolysis. The reaction was specifically designed to complement the popular amide coupling reaction.

Here, we show for the first time that isocyanides can be alkylated by a S_N2 mechanism through a nitrilium ion with concomitant hydrolysis to the corresponding amide. In this novel 3-component reaction, the isocyanide can be described as a Umpolung-derived rare amide carbanion synthon. The use of isocyanides as acyl anion equivalents provides a conceptually innovative approach to amide synthesis. As isocyanides are most commonly derived from either primary amines or aldehydes or ketones, the new reaction connects a primary amine via a formyl-*C* to an alkyl halide or in the second case an aldehyde or ketone carbonyl is connected through the formamide-*C* to an alkyl halide. The position of the amide group in the classical amide coupling of amines and carboxylic acids and the herein described isocyanide/alkylation derived amides are different. By repurposing halide building blocks as amides, instead of the classic amide, a subtle change in synthetic accessibility emerges. Attempting to synthesize the same molecules by the two orthogonal methods, large scale data analysis of educts reveals a great disadvantage of the classical method, since the required carboxylic acid building blocks are more difficult to access, not available at all, and more expensive than the corresponding alkyl halides by an average factor of 2.5. We also performed a survey of commercial availability of the required building blocks from a commercial vendor catalog (Fig. 7E), which revealed that 3.8 million amides are accessible by the classical method and 4.2 million by the new method, with only 1 million matched molecular pairs between the two sets. A chemoinformatic analysis of commercial building blocks demonstrates that by utilizing halides and primary amine-, aldehyde-, or ketone-derived isocyanides, our method more than doubles the available amidation chemical space. There is minimal overlap of chemical space compared to the classical amide coupling, demonstrating that a halide-isocyanide amidation can provide broad access to new and complementary structures. Repurposing of halide and isocyanide building blocks provides an enormous opportunity to expand the accessible chemical space or amides, because halide and amine or aldehyde/ketone feedstocks are typically low cost and available in high diversity. A halide-isocyanide amidation would therefore leverage the abundance of one popular building block and easily to access isocyanides from other popular building blocks. Collectively, these analyses quantify the value that a halide–isocyanide amidation would provide as an addition to the synthetic toolbox. High-throughput experimentation was used to develop the reaction, along with classic scope studies, both of which demonstrated robust performance against many pairs of reactants. The new reaction can be

carried out under practical, mild conditions with yields ranging from good to moderate to poor, depending on the structure of the reactants. The functional group compatibility of the reaction is high. Late-stage functionalization of a drug is exercised. Alkyl halides are very frequently encountered in pharmaceutical research, so harnessing this functional group would also provide plenty opportunities for late-stage diversification. Upscaling of the reaction to gram scale have been shown. Complex otherwise difficult to access compound classes such a lipids, isoprenoids or functionalized amino acids can be synthesized by this method. Electrophilic alkyl halides are a cheap, abundant feedstock and are commercially available in high diversity, making them a valuable starting material for the amide synthesis. Similarly, isocyanides are accessible in two steps from abundant primary amines or ketones or aldehydes. In conclusion, we have successfully developed an efficient new way to form amides, by reacting isocyanides, alkyl halides, and water in a three-component fashion. Our innovative amide synthesis will be of potential use in the synthesis and discovery of novel bioactive molecules. It is beyond current amide bond forming methods and with its unusual synthon features, exponential complexity increase, and its wide scope, it will allow to scout novel chemical space hitherto inaccessible.[32] It is conceivable that other nucleophiles than water can also react with the intermediate-formed nitrilium ion in this new multicomponent reaction, and work is currently underway in our laboratory to broaden the range of nucleophiles.

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Figures

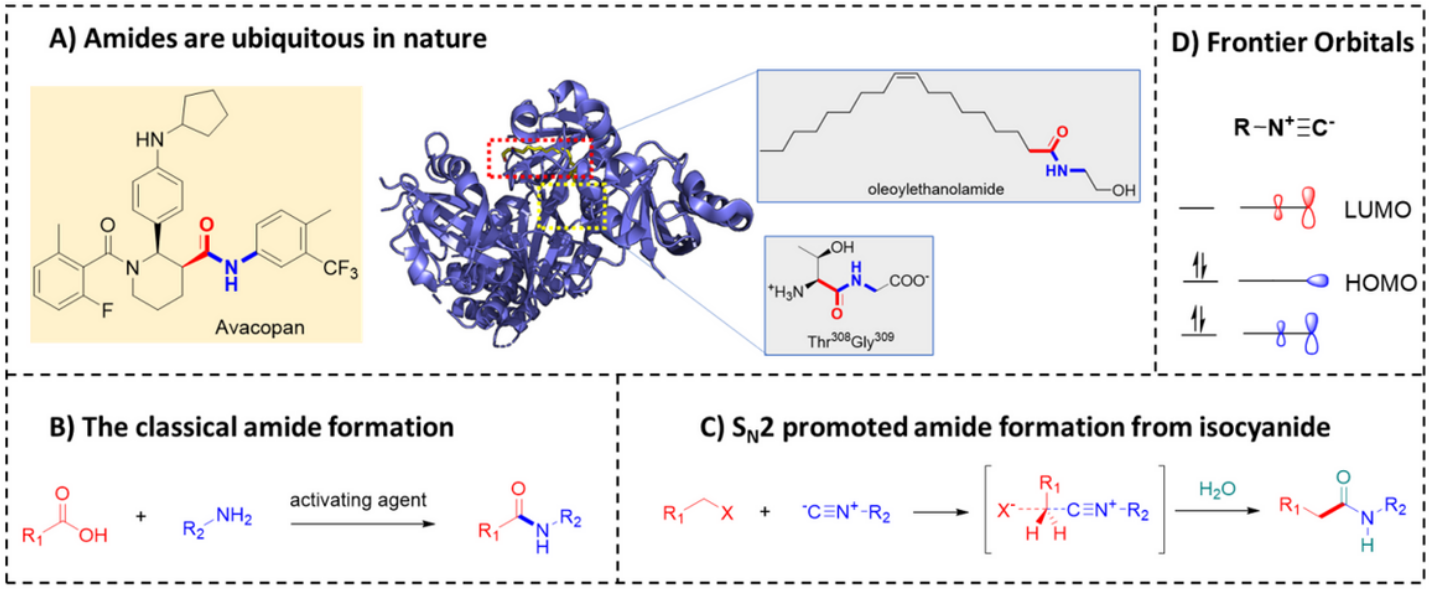

Figure 1

Background and motivation for novel amide formation. A) Amides are ubiquitous in nature: autoimmune disease drug Avacopan and transcription factor hypoxia-inducible factors HIF-3α (PDB-ID 7V7W) with natural ligand oleoylethanolamide. B) The classical approach to amide formation involves stoichiometric activation/coupling of carboxylic acid and amine. C) The novel multicomponent reaction amide synthesis involves an S_N2 promoted *C-C* coupling reaction, followed by hydrolysis of the nitrilium ion. D)

Frontier orbitals of the isocyanide to rationalize chameleonic behavior as a *C*-nucleophile and *C*-electrophile.

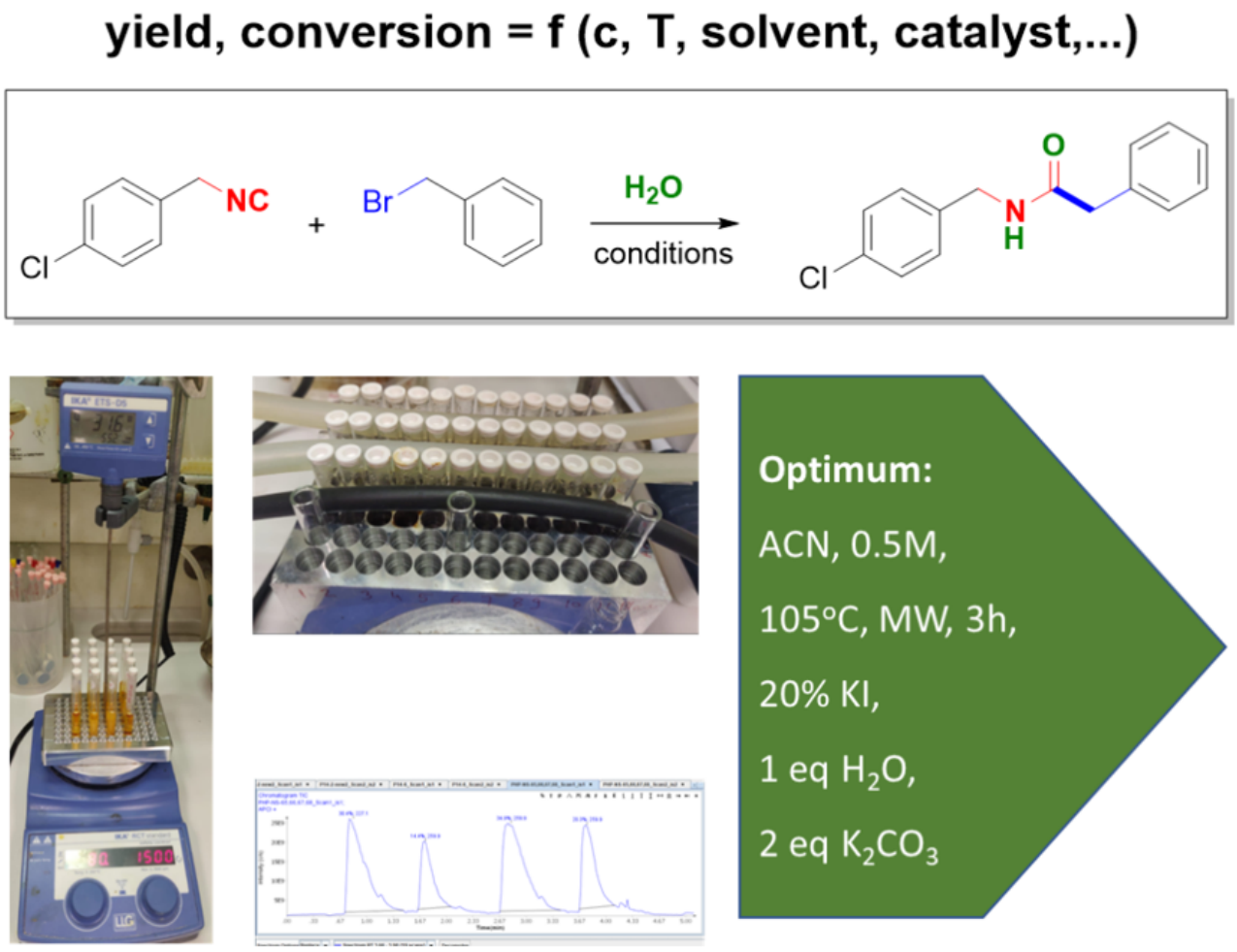

Figure 2

Optimization of reaction parameter using high throughput experimentation. Scheme of the model reaction, parallel heating in a metal block, and stagged HPLC injections.

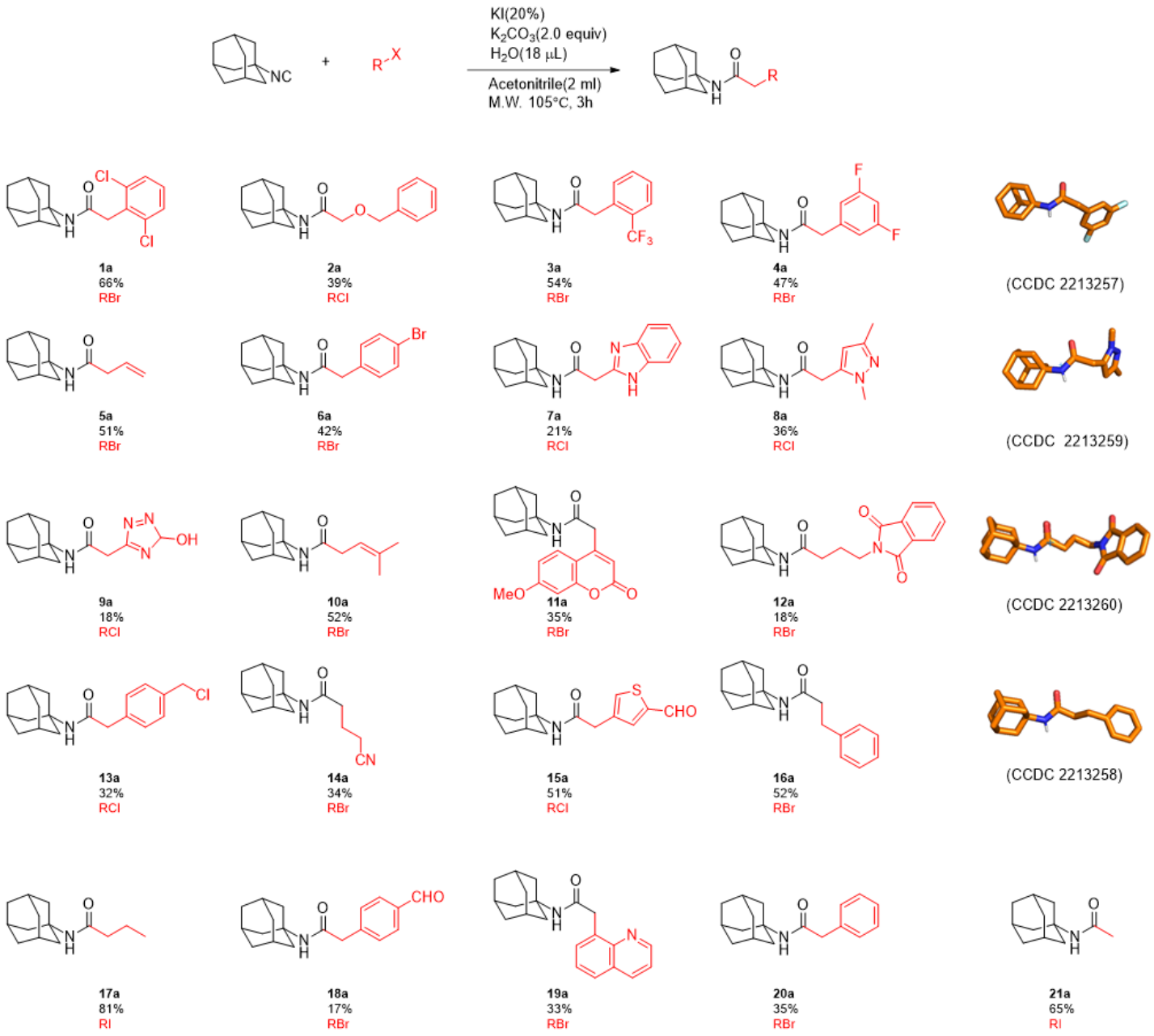

Figure 3

Scope of the halide electrophile with adamantyl isocyanide as the fixed component. Several stick presentations of X-ray structures and their CCDC codes are given.

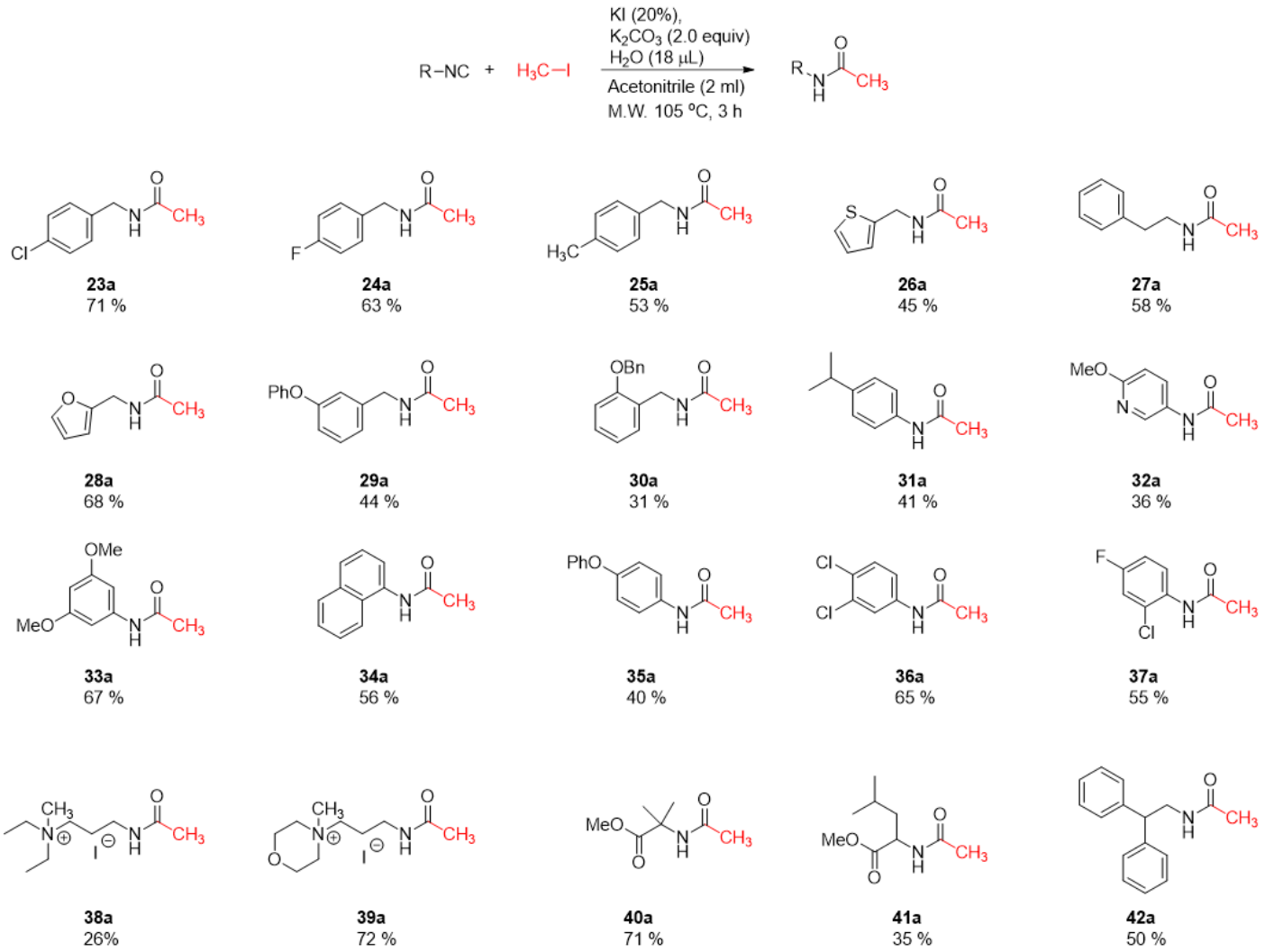

Figure 4

Scope of the isocyanide nucleophile with methyl iodide as the fixed component.

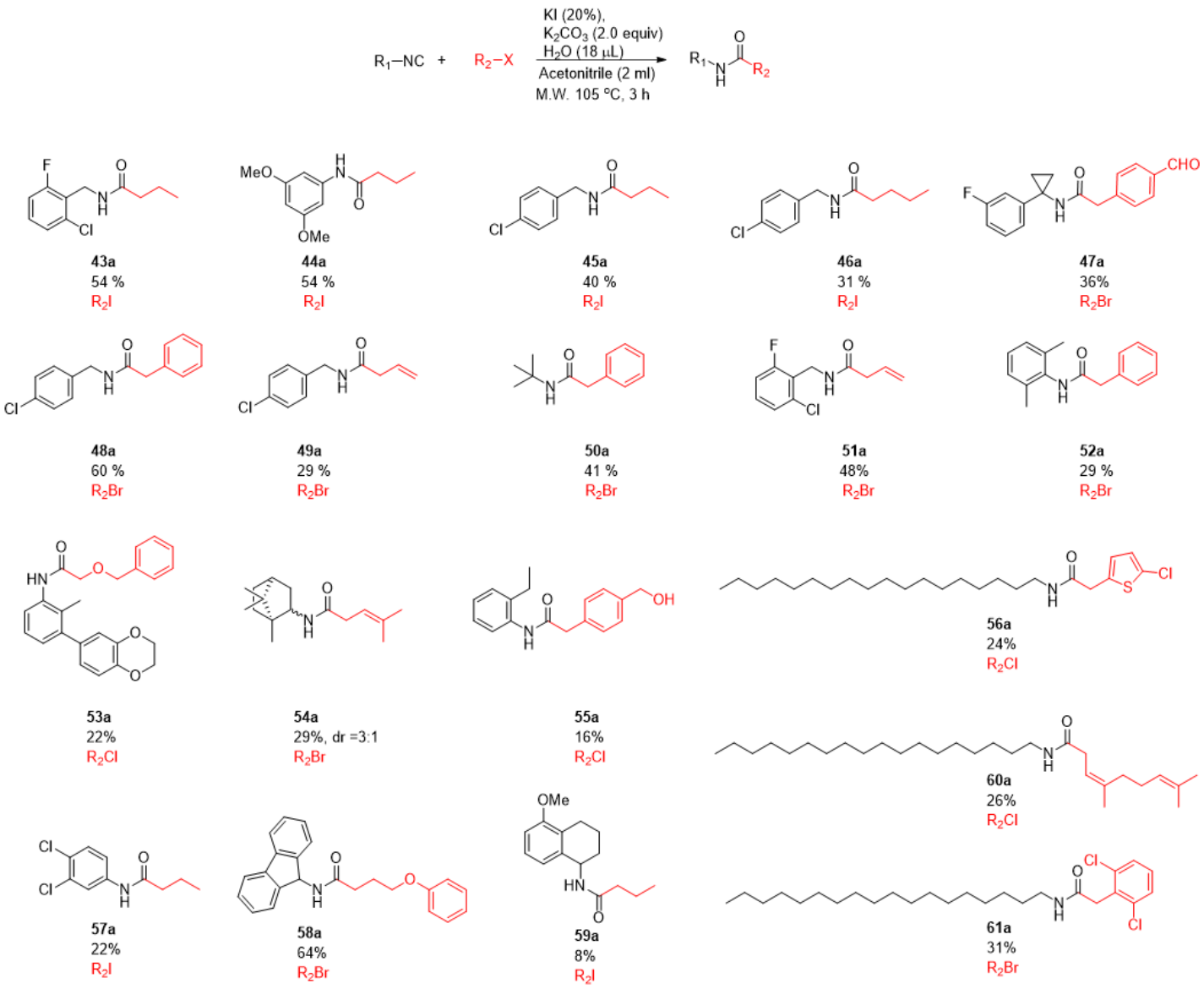

Figure 5

Mixed reaction examples of the isocyanide nucleophile with the alkyl halide.

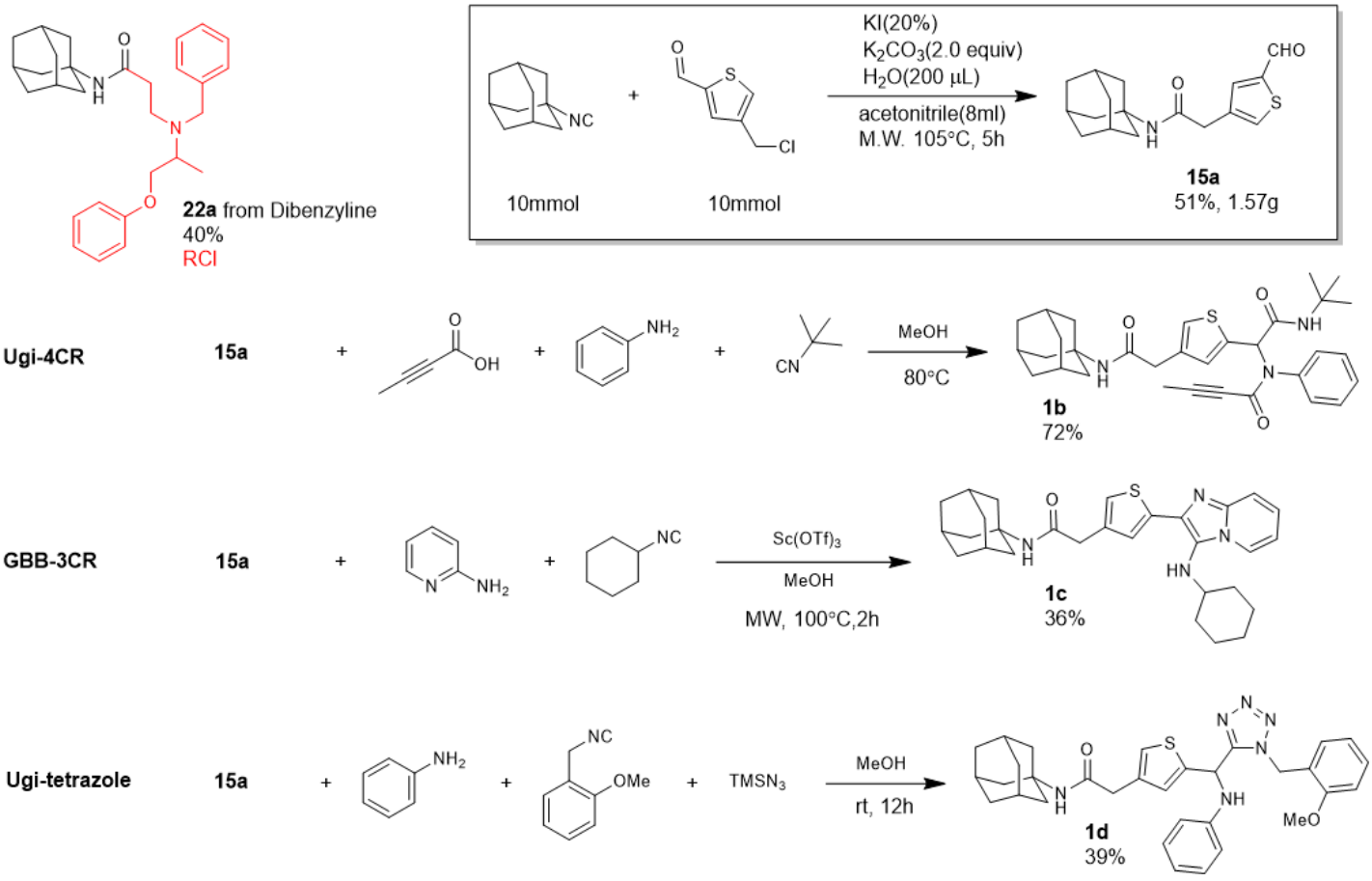

Figure 6

Late-stage diversification, scale-up and some follow-up chemistries.

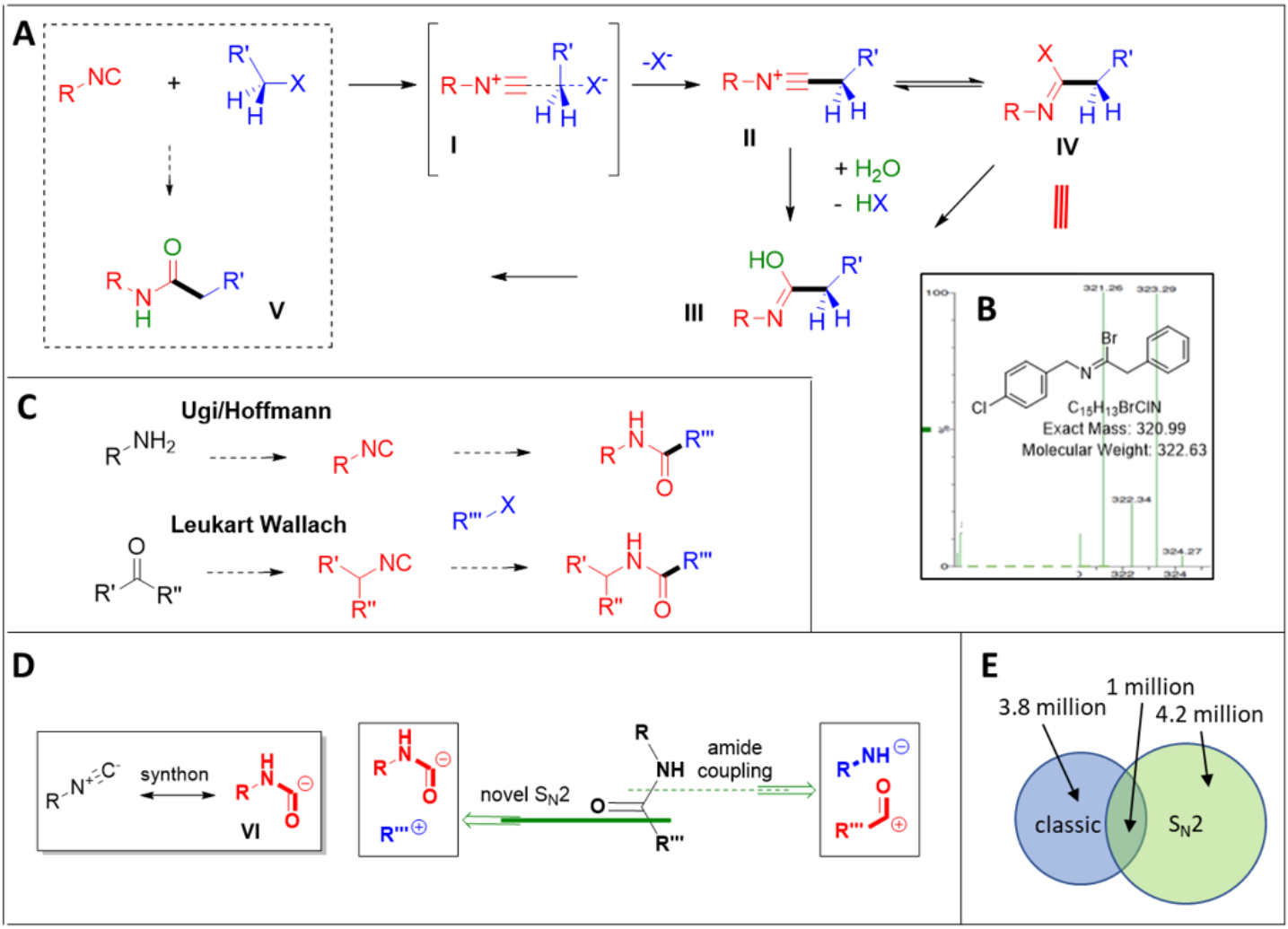

Figure 7

Proposed mechanism and evidence, RNC synthon, retrosynthetic valuation, and comparison with the classical amide coupling. A) Proposed mechanism and MS evidence of an imidoyl bromide intermediate (B). C) Most popular and efficient access to isocyanides by two different synthesis pathways. D) Comparison of the classical and the S_N2-based amide formation and the amide carbanion isocyanide synthon. E) Venn diagram for chemical space analysis of the classical and S_N2-based amide formation and its overlap.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FinalSN2SI.docx