SYNTHESIS OF *N*-SUBSTITUTED ARYL AMIDINES BY STRONG BASE ACTIVATION OF AMINES

by

MUHAMMAD M. KHALIFA

A THESIS

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Professor Michael M. Haley

This project describes an efficient method for the direct preparation of *N*-substituted aryl amidines from nitriles and primary amines. The method employs activation of amines by a strong base and provides greater access to a pharmaceutically relevant functional group. The creation of functionalized amidines and salient amidine-containing moieties via the newly described route was explored. This synthetic approach tolerates deactivated nitriles, nitriles with competing nucleophilic aromatic substitution sites, and aryl amines. Serial amidine formation is also possible, leading to new routes for the creation of tetrahydropyrimidines, benzimidazoles, and bis-amidines. The method described herein features superior yields, improved material and time economy, and greater starting material compatibility compared to other established routes of amidine synthesis. Additionally, this project led to the creation and characterization of six compounds hitherto undescribed in the literature.

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Background

This project outlines a new method for the creation of *N*-substituted amidines from nitriles and amines. It provides a new tool for synthetic organic chemists interested in producing these types of compounds. Understanding what amidines are, how and why they are used, and the most common methods for preparing them prior to the undertaking of this project is important for a full understanding of this project and its relevance. A glossary clarifying chemistry terms that may be unfamiliar to the layperson has been provided at the end of this work; terms defined in the glossary are underlined at their first appearance in the text.

Amidines and Amidine Nomenclature

The amidine functional group is a molecular motif featuring a central carbon atom singly bonded to one nitrogen atom and doubly bonded to a second nitrogen atom (Figure 1).

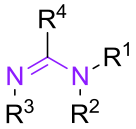


Figure 1: The amidine functional group

Amidine motif (purple) in a generic molecular context. By convention, carbon atoms are omitted for clarity and "R" groups stand in for any atom.

Compounds whose molecular structure contains one or more of such functional groups can be generically termed "amidines".

In Figure 1, the R groups attached to the atoms of the amidine group stand for any atom that may be attached to such an amidine. When these R groups represent anything but hydrogen atoms, they are termed "substituents". The resulting amidine is

appropriately termed a "substituted" amidine, since "substitutions" have been made in place of the hydrogen atoms present in an "unsubstituted" amidine. Note that R^4 in Figure 1 is attached to the carbon, and for the purposes of this project represents the remainder of the molecular structure, i.e., the structural context to which the amidine is attached. The focus of this project is on *N*-substituted amidines, which are amidines with substitutions attached to the nitrogen atom(s). For this reason, further discussion of R groups and substitutions does not apply to R^4. For substitutions, the prefixes "mono", "di", and "tri" indicate the extent of substitution. Di-substituted amidines may be further classified as "symmetrical" or "unsymmetrical": a symmetrical di-substituted amidine contains one substituent on each of the nitrogen atoms, though the substituents need not be identical to each other. Accordingly, a di-substituted amidine with both substituents attached to the same nitrogen atom, whether or not the substituents are equivalent, is considered unsymmetrical.[1] These relationships are summarized in Figure 2. A molecule containing multiple amidine motifs is denoted by the prefix "bis", "tris", etc. This project does not address compounds with more than two amidine motifs, i.e., only mono- and bis-amidines are discussed.

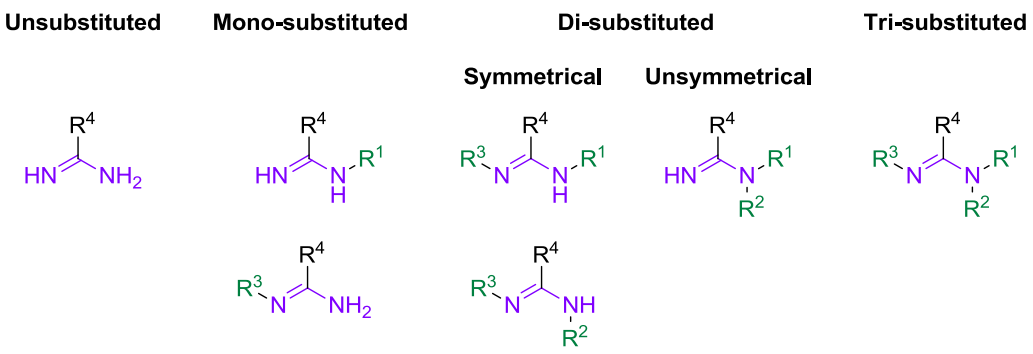


Figure 2: Amidine nomenclature

Core amidine motif (purple) with substituents (green) determining amidine nomenclature highlighted. This project focuses primarily on mono-substituted and/or bis-amidines.

LEGO® building blocks can serve as an appropriate metaphor for organic chemistry: Though simple combinations of a few elemental blocks (one carbon atom and two nitrogen atoms) yield important structural similarities (the amidine functional group), combining such motifs into larger structures leads to myriad possibilities in the features and properties of the resulting creations. Synthesis of new compounds is modular, and this modularity is important to manipulating the properties of all types of compounds, amidines included. We have already defined the central feature of amidines, i.e. what makes an amidine an amidine. We have also briefly discussed sources of diversity within the amidine family, i.e., what differentiates amidines from each other. This project examines synthesis of a specific subset of amidines; using the introduction to amidines previously described, we will now define the subset of amidines in question.

Amidines share a number of properties because of their structural commonality, but the effect of substitutions can vary widely depending on the type and extent of substitution(s). The nomenclature of amidines reflects the nature of these substitutions.

In this project, we focus specifically on the creation of *N*-substituted aryl amidines; thus the amidines discussed here are substituted, as previously defined, and specifically so at the nitrogen atoms. The amidines themselves are attached by their central carbon to a distinctive molecular feature, the aryl ring (Figure 3), and therefore fall in the family of "aryl amidines".

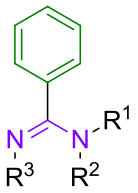


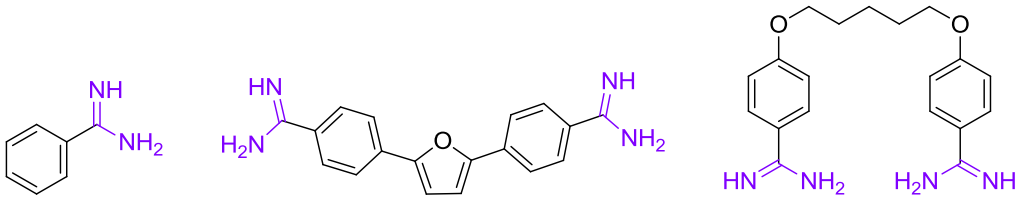
Figure 3: Aryl amidine generic structure

Aryl amidines are characterized by an amidine motif (purple) appended to an aryl ring (green). This project examines preparation of *N*-substituted aryl amidines.

The importance of this subset of amidines will be discussed in the following sections.

Pharmaceutical Relevance of Amidines

In addition to a number of applications in material chemistry and organic synthesis, amidines are of great importance to pharmaceutical chemistry.[2-6] Benzamidine (Figure 4), the simplest aryl amidine, is a specific inhibitor of trypsin and related serine proteases; its derivatives act as antimicrobial and antiparasitic agents and have been used for the treatment of a variety of diseases, including pneumocystis pneumonia, antimony-resistant leishmaniasis, and human African trypanosomiasis for over fifty years.[7-9]



Benzamidine **Furamidine** **Pentamidine**

Figure 4: Benzamidine and its most important derivatives

These unsubstituted amidines (purple) continue to be pharmaceutically relevant.

Amidines are known to bind nucleic acids; such action is crucial to their mechanism of action in some disease models.[10-13] This property of amidines has been known for some time, and modulation of long, amidine-containing compounds has been proposed for sequence-specific targeting of both RNA and DNA.[14]

Amidines and larger amidine-containing molecular motifs have recently been evaluated for their anti-cancer and analgesic properties, and extensive literature precedent exists for their importance to medicinal chemistry.[15-17] In addition to the established uses for amidines, furamidine (Figure 4) is currently in Phase II trials for use against malaria, and derivatives of pentamidine (Figure 4), especially *N*-substituted derivatives, show promise for use against myotonic dystrophy type 1.[8, 18-20] Additionally, several large, amidine-containing functional groups possess important pharmaceutical properties in their own right.

Benzimidazole derivatives have been investigated for their anthelminthic and antifungal activity; a new class of benzimidazole derivatives has been identified as antimalarial lead compounds (Figure 5, top row).[16, 21-23] Tetrahydropyrimidine derivatives display properties relevant to treating symptoms of Alzheimer's disease and can act as neuromuscular blocking agents (Figure 5, bottom row).[18, 24-25]

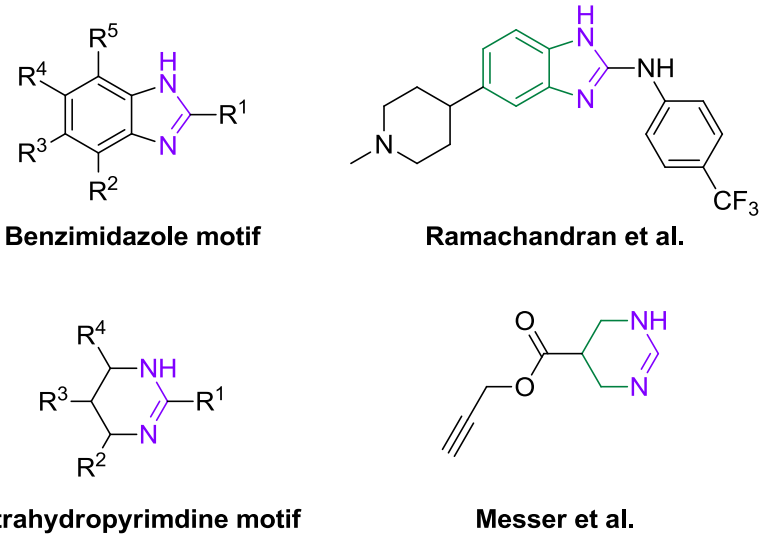


Figure 5: Amidine-containing moieties and pharmaceutically relevant derivatives

Benzimidazoles and tetrahydropyrimidines can be viewed as substituted amidines. Generic structures are given along with the pharmaceutically relevant derivative; motifs are highlighted in context (green).

Both motifs can be considered *N*-substituted amidines. These findings, in conjunction with preceding literature on amidines, point to the importance of *N*-substituted amidines in pharmaceutical chemistry. This pharmaceutical relevance is the impetus for studying new examples of *N*-substituted amidines and methods for amidine synthesis.

Amidine Synthesis in the Literature

Discussion of amidines and their study necessarily demands an examination of how amidines are synthesized, since it is the creation of amidines that makes feasible their study for use as potential therapeutics against human disease. It is therefore important to understand the challenges associated with amidine synthesis, the most common methods for amidine preparation, and the limitations these methods present in the context of producing new, pharmaceutically relevant *N*-substituted amidines.

Amidines are a broad class of compounds, and whole books have been written on their synthesis and chemistry.[1] Because of the scope of this project, we will examine only the synthesis of *N*-substituted amidines. In particular, the creation of new *N*-substituted amidines for study necessitates functionalization of the amidine group. The most fundamental barrier to the creation of *N*-substituted amidines is the inaccessibility of amidines via direct addition of the simplest starting materials, amines and nitriles.[26] To overcome this barrier to amidine formation, several strategies have been established in the literature.

Nitrile Activation via Electron-withdrawing Substituents

Nitriles can be activated by substitution with electron-withdrawing groups to make them more reactive towards addition by an amine.[1, 26] While effective, this method necessitates introducing functional groups to the structure of the nitrile starting material that are then incorporated, perhaps undesirably, into the structure of the amidine product. In addition, such activating groups may possess cross-reactivity with amines and preclude amidine formation. Thus the applicability of this strategy is limited in its range of compatible starting materials, and limits the menu of accessible products.

Nitrile Activation via Acidic Conditions

Nitriles lacking electron-withdrawing groups can be activated at high temperatures in the presence of Lewis acids, or transformed into intermediates under acidic conditions in a preceding step before subsequent addition of the amine.[1, 26] These acidic conditions have several disadvantages for use in *N*-substituted amidine synthesis.[26] Amidine functionalization is limited by the compatibility of amine starting materials with acidic conditions, and cross-reactivity can become a problem when

complex *N*-substitutions contain other functional groups. Methods employing acidic conditions, such as the Pinner reaction, typically feature poor yields (<40%) of amidine.[27] Often requiring multiple synthetic steps, these reactions are cost-prohibitive in terms of both time (the Pinner method requires a minimum of 48 hours for the first step) and materials (10:1 ratio of amine to nitrile).[27]

Amidine Synthesis via Transition Elements and Metals

Amidine formation may also be achieved through the use of transition elements and catalysis with metals.[1, 17, 26-27] Unactivated nitriles react readily with aluminum amides, and lanthanide (III) triflates have been used to form amidines via a condensation reaction.[1, 26-27] Apart from the relative adverse environmental impact of transition metal chemistry, these strategies have a number of limitations in regards to *N*-substituted amidine synthesis. Aluminum amides are harsh reagents, and share issues of starting material compatibility and cross-reactivity with other methods for amidine synthesis. Mono-substituted amidines are inaccessible through lanthanide (III) triflate catalyzed condensation, and their compatibility with secondary amines is limited.[26] Rousselet *et al*. described a method for amidine synthesis from unactivated nitriles and amines using copper. The strategy successfully addressed a number of the limitations previously discussed; however, the method is incompatible with aromatic amines, and is therefore also limited.[26]

Synthetic accessibility of a wide range of *N*-substituted amidines is of critical importance to studies attempting to develop amidine-based pharmaceutical therapeutics for a variety of human diseases. The limitations of established methods of amidine synthesis therefore present a significant barrier to the progress of such studies. A

method for preparation of amidines that addresses issues of starting material compatibility, functional group cross-reactivity, time and material economy, environmental considerations, and product accessibility would represent an important step forward in the fields of organic and pharmaceutical chemistry.

A New Approach to Amidine Synthesis

Though amidine preparation via the addition of a deprotonated amine to a nitrile has been described in the literature, the approach is not well studied.[8, 28-29] Sanger, and later Boeré, used deprotonated amines to prepare trimethylsilyl amidines that could then be converted to the corresponding unsubstituted amidines.[28-29] It should be noted that Boeré *et al*. reported that their method was incompatible with starting materials capable of undergoing carbanion formation via a ketamine-enamine tautomerization, such as those bearing a hydrogen or a chlorine atom in the α-position relative to the nitrile[1].[28] The accessibility of unsubstituted amidines under basic conditions as described in the literature provides a precedent for investigating the creation of substituted amidines by a similar approach. Creation of a nucleophile by strong base activation of an amine presents the possibility of preparing a wider range of *N*-substituted amidines in less synthetic steps and without the use of transition metals; however, such a method's compatibility with starting materials, its chemoselectivity, and its synthetic efficiency are unknown.

The importance of improved routes to new *N*-substituted amidines necessitated the development of amidine synthetic methodology that overcomes or minimizes the

1 The details of carbanion formation and ketamine-enamine tautomerizations are not relevant to this project, and so have not been explained for the layperson. It is sufficient to understand that limitations exist for Boeré's synthetic method that may be addressed in ours.

limitations of existing strategies. Amidine synthesis under basic conditions, i.e. via activation of amines by strong base, showed promise as a candidate for improved amidine synthetic methodology. Here, we outlined a method for preparing *N*-substituted aryl amidines under basic conditions and used it to synthesize two series of representative amidine targets in an effort to establish the synthetic relevance of the method by delineating its compatibility with starting materials, its chemoselectivity, and its synthetic efficiency. We further demonstrated that larger, amidine-containing moieties are accessible via our method of synthesis. In the course of this study, we were also able to prepare and characterize six new amidine species that had not been previously described in the literature. Featuring shorter reaction times, superior yields, better material and time economy, and greater compatibility with a broad range of starting materials, our method of amidine preparation by strong base activation of amines makes accessible a host of new *N*-substituted amidines for study against a variety of human diseases.

Methods and Materials

This project sought to develop and test a new method for the preparation of *N*-substituted amidines from nitriles and amines. The strategy was adapted from literature precedents showing that deprotonated amines with trimethylsilyl substituents are sufficiently nucleophilic to add to aryl nitriles, and can then be converted to unsubstituted amidines.[28-29] Thus we developed simple conditions for the generation of deprotonated amines and tested the accessibility of *N*-substituted amidines via this route using a range of amine and nitrile starting materials. Amidine accessibility was assessed by attempting synthesis of a given amidine target, isolating the products of the reaction, and characterizing the resultant materials. Experimental yields of amidine were calculated, and average experimental yields were used as a measure of synthetic accessibility of the amidine under the given reaction conditions.

Methods

The following section describes general procedures for different steps in the experimental process. In the first step, the target amidines are created under as similar conditions as possible by activation of the appropriate amine starting material with a strong base before introducing the nitrile starting material. The reactions are allowed to proceed for a maximum of 24 hours before quenching. A variety of processes are used to separate the resulting mixture into its components and to purify the isolated components. Components are subjected to three forms of characterization to determine identity and purity, at which point the amount of each compound produced can be determined and the yield of each product calculated. A general and accessible

explanation of the most relevant processes pertaining to synthesis, purification, and characterization is herein provided; common laboratory techniques have not been described for brevity's sake, and because more authoritative sources are available.

Reaction Conditions

All reactions are performed entirely at room temperature in a water-free environment under an inert atmosphere of pure nitrogen gas. Tetrahydrofuran (THF) is used as a reaction solvent to prevent nitrile trimerization.[28] A visual overview of the reaction process is provided in Figures 6-8; details of each step are provided below.

Amine Activation

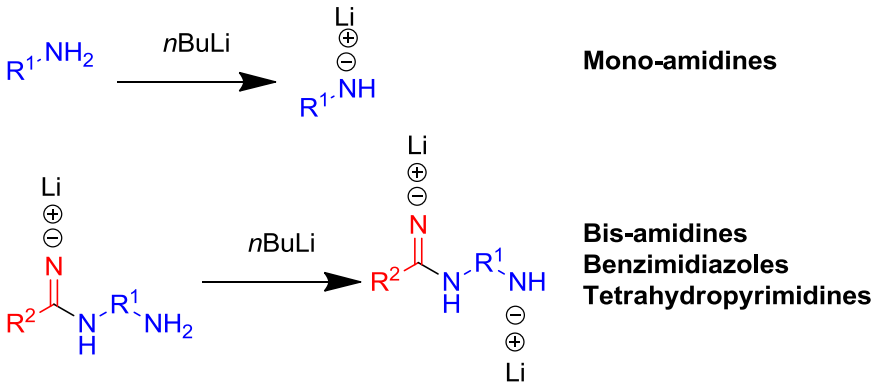


Figure 6: Amine activation

Amines (blue) are activated by *n*-butyllithium to form lithium amine salts. These are highly nucleophilic due to the negative charge on the nitrogen. In bis-amidines, benzimidazoles, and tetrahydropyrimidines, a second activation step is required after addition of the nitrile (red) [nitrile addition not shown].

Under the reaction conditions described above, amines are activated by the introduction of *n*-butyllithium (*n*BuLi), a strong base, and allowed to react for approximately 15 minutes. This process removes a hydrogen nucleus from the amine and makes it more reactive towards addition with a nitrile; it is sometimes accompanied by a color change

or formation of a precipitate. In reactions where the target contains only a single amidine group, the strong base is added in a 1:1 ratio relative to the amine. In reactions where the target is a bis-amidine, benzimidazole, or tetrahydropyrimidine, the *n*BuLi is ultimately added in a 2:1 ratio relative to the di-amine starting material. After the initial activation and subsequent nitrile addition/amidine formation, a second round of amine activation is performed. This allows formation of the desired benzimidazole or tetrahydropyrimidine product, or precedes a second round of nitrile addition for creation of bis-amidines.

Nitrile Addition & Amidine Formation

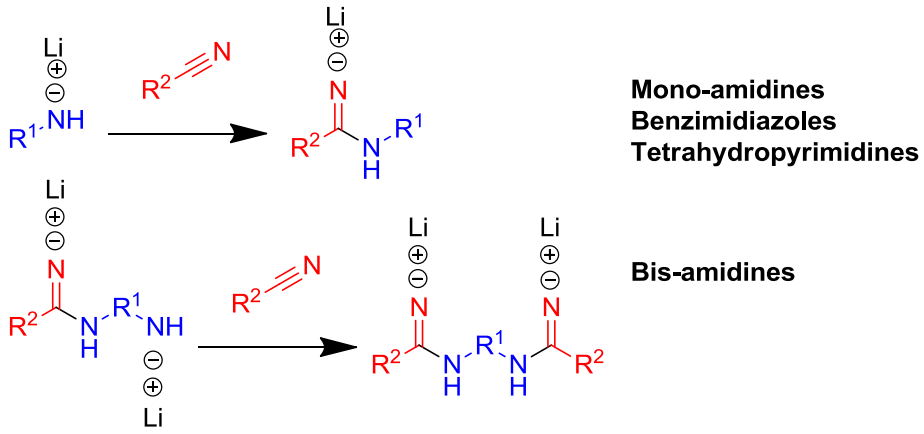


Figure 7: Nitrile addition

The activated lithium amine salt adds readily to the nitrile (red) to form the lithium amidine salt. In bis-amidines, a second nitrile addition step is required after the second round of amine (blue) activation [amine activation step not shown].

Following amine activation, one equivalent of nitrile in a small volume of solvent is added to the reaction mixture. In reactions where the desired product is a bis-amidine, a second equivalent of nitrile is ultimately added after a second round of amine activation. In such cases, and in cases of benzimidazole and tetrahydropyrimidine formation, one

hour of reaction time is allowed for the first round of amidine formation before the second round of amine activation is performed. After the final equivalent(s) of nitrile are added, the addition reaction is allowed to stir overnight, and is sometimes accompanied by further color change and/or formation of precipitate. Finally, the reaction is stopped with an acidifying quench.

Reaction Acidification & Quenching

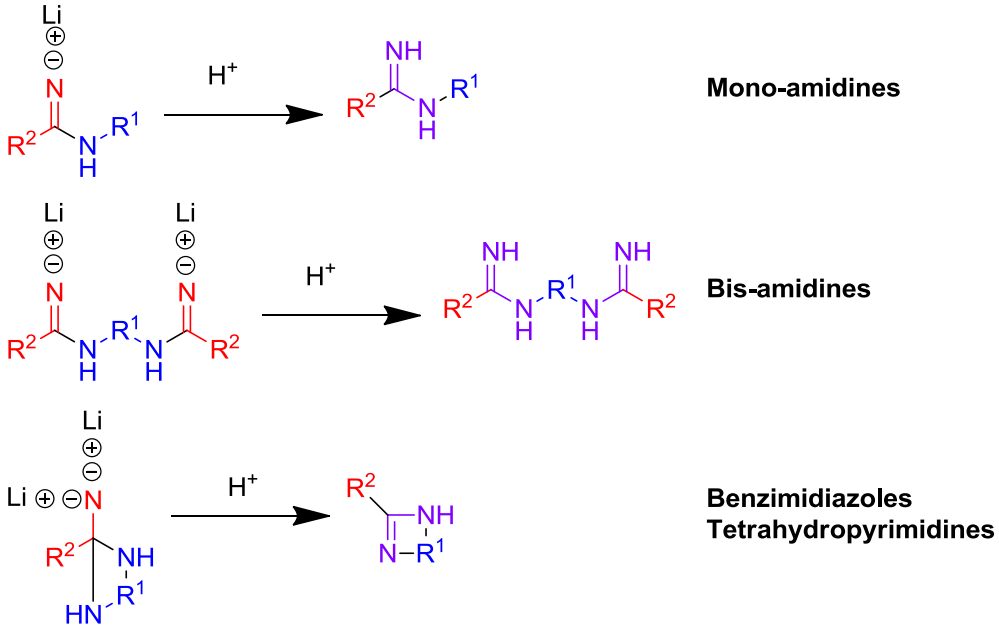


Figure 8: Acidifying quench

The lithium amidine salt is converted to the desired amidine (purple) by addition of ethanolic HCl. In benzimidazoles and tetrahydropyrimidines, the acid quench eliminates ammonia to give the cyclic desired product.

The lithium amidine salt is protonated with an anhydrous acid (HCl in ethanol), converting it to the desired amidine. In benzimidazoles and tetrahydropyrimidines, the acidic quench leads to the elimination of ammonia to give the desired product. The

acidic quench serves to neutralize any remaining base in the reaction mixture, and in strong concentrations gives the HCl amidine salt, which aids isolation and purification.

Product Purification

Following the acid quench, the desired amidine product must be separated from impurities in the crude reaction mixture. This can be achieved through a number of methods, which are often used in combination with one another to obtain the purest possible sample of amidine for characterization.

Precipitation and Filtration

The desired amidine is usually produced in the form of a hydrochloride salt, which is soluble in the quenched reaction mixture but insoluble in ether. Large quantities of ether are added to the reaction mixture, and the desired product often precipitates from solution as a solid. Cooling facilitates precipitation of product, which can then be separated from the solution by vacuum filtration and dried. In some cases, this is sufficient to give the pure amidine product. Purity and identity of the isolated compound are determined by proton (^{1}H) and/or carbon-13 (^{13}C) NMR (see "Product Characterization"). If the product is deemed insufficiently pure, it can be purified by chromatography and/or recrystallization. These processes are discussed in the sections that follow.

Chromatography

Column chromatography is used to separate mixtures of compounds and isolate products in desired purity. This process involves separating the desired product from the rest of the reaction mixture by dissolving all components in a liquid and washing them

through silica gel. Different compounds have different physical properties, which affect their affinity for the gel and their ability to dissolve in the liquid phase. These differences in solubilities and affinities result in physical separation of different compounds as they travel through the gel. Serially collecting fractions of the liquid phase gives portions containing only a single species; these are combined and the pure species isolated for characterization.

Recrystallization/Lyophilization

Recrystallization from an acidic solution can produce crystals of pure compound, though effective recrystallization conditions are not always available. When possible, recrystallization is a preferred method for product isolation because it obviates column purification, which can be much more time consuming. Recrystallization also gives fully protonated HCl amidine salts, which are more easily recognizable via the characterization methods used. For a similar reason, lyophilization from an acidic solution is used on compounds purified by other means to give dry, fully protonated HCl amidine salts for characterization.

Product Characterization

Characterization of the reaction products demonstrates the purity and identity of the amidines isolated. By characterizing each isolated target, we establish the success of our synthetic method and provide a means to verify the identity of products created in the future. In the case of previously undescribed compounds, our characterization is the first experimental data available regarding these compounds.

^{1}H Nuclear Magnetic Spectroscopy

Primary characterization of amidine products is achieved by ^{1}H nuclear magnetic spectroscopy (NMR). NMR analysis is analogous to an MRI for molecules. The process involves subjecting samples of compound to strong magnetic fields and measuring the response of atomic nuclei (in this case, the hydrogen nuclei). The nuclei's responses depend heavily on their chemical environment, which is in turn determined by the molecular structure of the compound in question. The data obtained from NMR analysis allows us to create a fingerprint-like image that is unique to each compound. Analysis of these images helps determine whether the compound obtained is the desired product based on similarity of the imaged "fingerprint" to the expected "fingerprint". This initial analysis gives vital information regarding sample purity and identity. When a compound appears to be the pure desired product by ^{1}H NMR spectroscopy, it is further characterized by ^{13}C NMR analysis.

^{13}C Nuclear Magnetic Spectroscopy

Secondary characterization of products is achieved by ^{13}C NMR analysis. ^{13}C NMR analysis works in the same way as ^{1}H NMR, but with a focus on carbon nuclei. Combined with the information given by ^{1}H NMR, ^{13}C NMR data can verify the identity and purity of a given compound sample. When ^{13}C NMR corroborates the ^{1}H NMR determination of purity and probable identification for a desired product, the sample is sent to an external laboratory for analysis by high-resolution mass spectrometry; this is the final step in compound identification and characterization.

High Resolution Mass Spectrometry

High-resolution mass spectrometry allows highly precise mass measurements of the molecules in a sample. Since the expected mass of the amidine targets is known, a sample of compound can be analyzed to determine whether or not it contains molecules of that exact expected mass. Mass spectrometry does not determine compound purity; it only corroborates identity. If a sample is judged to contain molecules of the desired product by mass spectrometry, and the ^{1}H and ^{13}C NMR data reflect the desired product's structure with no impurities or contaminants, the target can be safely considered accessible by our method of synthesis. Once this determination has been made, we perform a calculation of the yield of the desired amidine to obtain a quantitative measure of the target amidine's accessibility (and by extension, the compatibility of our reaction method with the starting materials used).

Yield Calculation

Yield calculations serve as a quantitative measure of success for the new method of amidine synthesis described. If the amount of starting materials used is known, the maximum amount of product obtainable can be calculated. This is used as a benchmark, and the mass of pure amidine product isolated is measured and expressed as a percentage of this theoretical maximum. This is termed the "experimental yield" of that reaction. Reactions are performed multiple times until a representative average can be calculated (at least three trials), and this average experimental yield is expressed as the efficiency of a given reaction with the stated starting materials. In the context of this project, the average experimental yields serve as a way to compare accessibility of different amidines and compatibility of starting materials with our procedure.

Materials

The following section describes the main materials used during the course of this project. Common lab equipment and supplies have not been included, but specific instruments for characterization, as well as materials crucial to the reaction and subsequent purification, have been enumerated.

Non-substrate Reagents

This section discusses the substances crucial to the project that are not considered starting materials for the creation of amidines. Most centrally, *n*-butyllithium served as the strong base activator for the amines used, and THF served as an appropriate media for carrying out the reaction. THF was distilled from sodium metal under a nitrogen atmosphere. Acetyl chloride and ethanol were used to generate ethanolic HCl, the anhydrous acid for quenching the reaction mixture.

Substrates

The following figures show the range of starting materials tested in this project. The purpose of this project was to develop a demonstrably successful method of amidine synthesis utilizing strong base activation of amines. To this end, three series of targets were produced to demonstrate amidine accessibility with different starting materials. In the first, a series of amines with a range of nucleophilicities were reacted with the same nitrile (Figure 9). In the second, a series of nitriles with a range of electrophilicities were reacted with the same amine (Figure 10). In the third, a series of diamines were reacted with the same nitrile to create bis-amidines, benzimidazoles, and tetrahydropyrimidines (Figure 11).

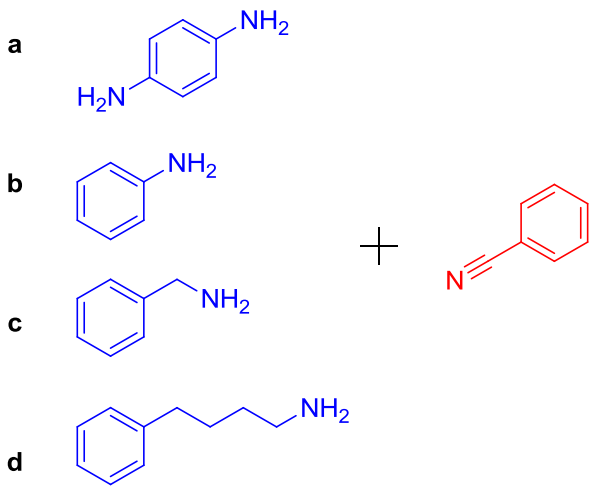


Figure 9: Starting materials for Mono-amidines Series 1

Four amines (blue) with increasing nucleophilicities (top to bottom) were reacted with the same aryl nitrile (benzonitrile, red) to assess amidine accessibility from amines with a range of reactivities toward nitriles.

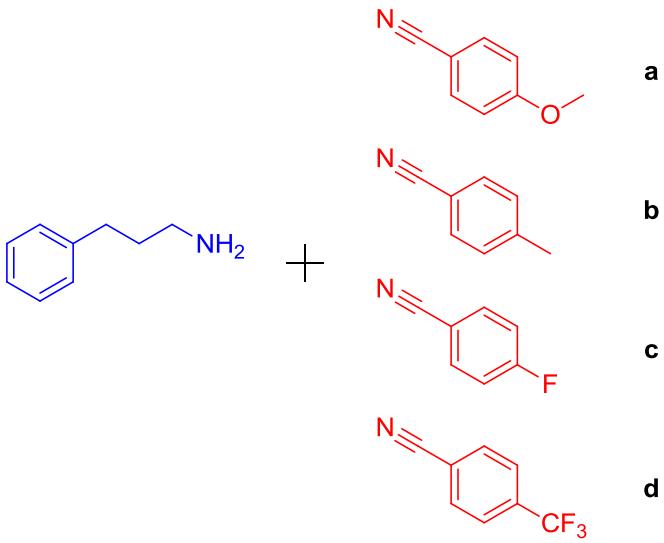


Figure 10: Starting materials for Mono-amidines Series 2

Four nitriles (red) with increasing electrophilicities (top to bottom) were reacted with the same primary amine (3-phenylpropylamine, blue) to assess amidine accessibility from nitriles with a range of reactivities toward amines.

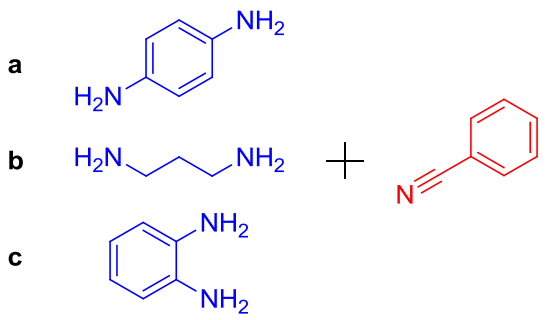


Figure 11: Starting materials for Diamine Series

Three diamines (blue) were reacted with the same aryl nitrile (benzonitrile, red) to assess feasibility of constructing larger amidine-containing moieties.

These series demonstrated the compatibility of our synthetic method with a wide array of substrates, and showed the method could be applied to the creation of more complex molecular features. The substrates chosen effectively represented the spectrum of starting material reactivities, and provided a measure of our method's applicability.

Purification & Characterization

Key materials used for purification included ether (Et_2O) for precipitating the desired products after their formation, and silica (SiO_2 and C18) for gel chromatography. Chromatography solvents were 0.01M aqueous HCl and ethanol. 1M and 10% aqueous HCl were used for recrystallization and lyophilization.

^{1}H and ^{13}C NMR spectra were recorded in d_6-DMSO using a Varian Mercury 300 MHz or 500 MHz NMR spectrometer with Prodigy multinuclear broadband cryoprobe. High-resolution mass spectra were recorded on a JEOL MS-Route mass spectrometer.

Experimental Results and Discussion

This project successfully developed a method for synthesis of *N*-substituted aryl amidines under mild conditions that features superior yields, greater material and time economy, and better compatibility with a wide range of starting materials. The method builds on a small body of existing literature for the synthesis of unsubstituted amidines, and demonstrates that strong base activation of amines is a viable approach to preparing substituted mono- and bis-amidines, benzimidazoles, and tetrahydropyrimidines. The pharmaceutical relevance of such species having been established, this project makes accessible a new menu of amidines for study, and thus contributes to the search for therapeutics against a variety of human diseases.

Mono-amidine Series 1: Exploring Amine Starting Material Reactivity

The first series of targets synthesized (Figure 12) demonstrated the range of nucleophilicities in amine starting materials that are compatible with this preparatory method. We prepared amidines from a deactivated aryl amine (Figure 12a), an aryl amine (Figure 12b), a benzylic amine (Figure 12c), and an effectively alkyl amine (Figure 12d). The average experimental yields over the best three trials were calculated.

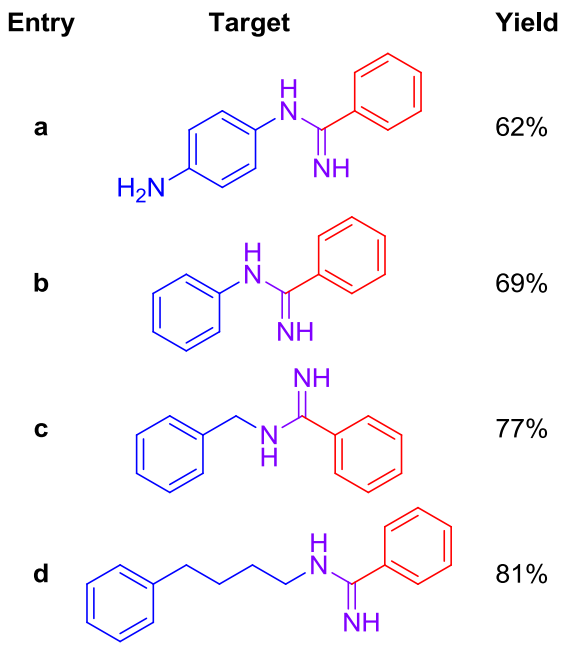


Figure 12: Mono-amidines Series 1

Mono-amidines (purple) were successfully synthesized from amines (blue) with a range of reactivity (increasing top to bottom) towards nitriles (benzonitrile, red).

The yields of these targets are markedly better via our method than those associated with *N*-substituted amidine preparation by acid activation of nitriles. As discussed previously, typical yields of methods such as the Pinner reaction are mediocre (<40%). Here, all target amidines are created in greater than 60% yield, which exceeds even some synthesis methodology via transition elements and metal catalysis. The most reactive amine affords the associated amidine in greater than 80% yield (Figure 12d); this product is a new compound that has not been previously described in the literature. Our method produces mono-substituted amidines readily (Figure 12a-d) and works well with aryl amines (Figure 12a-b). These features overcome the main limitations of synthesis methods via transition elements and metals.

Mono-amidine Series 2: Exploring Nitrile Starting Material Reactivity

The second series of targets (Figure 13) demonstrated the range of electrophilicities in nitrile starting materials that are compatible with our method of synthesis. We prepared amidines from deactivated aryl nitriles (Figure 13a-b) and activated aryl nitriles (Figure 13c-d). Additionally, one nitrile starting material contained a potential cross-reactive site (Figure 13c). The average experimental yields over the best three trials were calculated.

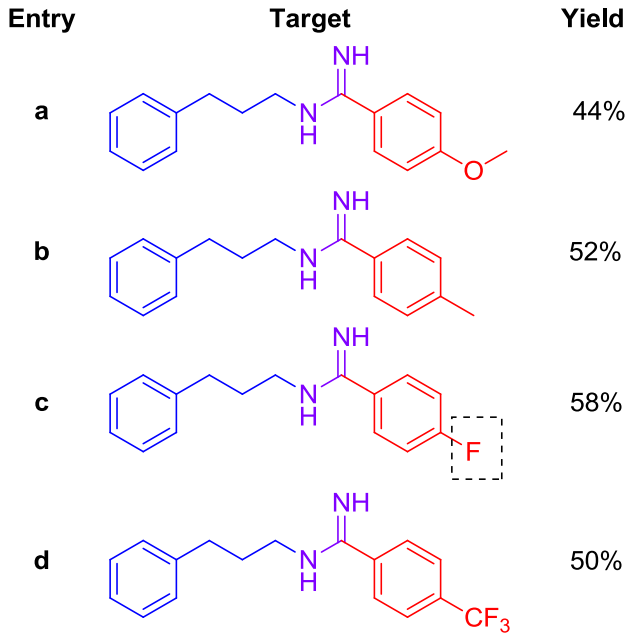


Figure 13: Mono-amidine Series 2

Mono-amidines (purple) were successfully synthesized from nitriles (red) with a range of reactivity (increasing top to bottom) towards amines (3-phenylpropylamine, blue).

The yields of these targets are only slightly better than those associated with *N*-substituted amidine synthesis under acidic conditions; nonetheless, several important features of our synthetic method were elucidated through this series. Firstly, amidines are comparably accessible from deactivated and activated nitriles via our procedure.

This is significant, since amidine synthesis from direct addition of amines and nitriles has been limited by the activity of the nitrile, as previously discussed. Additionally, *N*-substituted aryl amidine synthesis via strong base activation of amines is tolerated by a competing reactive site for nucleophilic aromatic substitution on the nitrile (Figure 13c, dashed outline). All amidine products in this series are novel, and have not been previously described in the literature. As in Series 1, mono-substituted amidines are readily accessible; our preparation overcomes the main limitation of amidine synthesis by lanthanide (III) triflates.

Diamine Series: Exploring Synthesis of Large Amidine-containing Motifs

The final series of targets (Figure 14) demonstrated the accessibility of bis-amidines, benzimidazoles, and tetrahydropyrimidines via our method of synthesis. We prepared a bis-amidine from a deactivated aryl diamine (Figure 14a), a tetrahydropyrimidine derivative from an alkyl diamine (Figure 14b), and a benzimidazole derivative from an aryl diamine (Figure 14c). The following yields were calculated over a single experimental trial, but are nonetheless worthy of discussion.

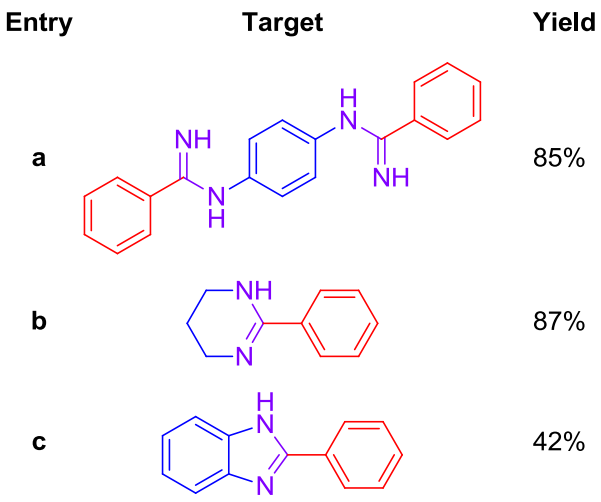


Figure 14: Diamine Series

Large, amidine-containing structural moieties were successfully synthesized from diamines (blue) and benzonitrile (red). Amidine groups highlighted (purple).

The yields for bis-amidine and tetrahydropyrimidine synthesis (Figures 14a and 14b, respectively) were high, even more so than for mono-amidines. The bis-amidine product (Figure 14a) was readily obtainable by precipitation, and required no further purification. Given the salience of bis-amidines in particular, this result indicates our method may be a superior route to *N*-substituted aryl bis-amidines for pharmacological studies. Synthesis of the benzimidazole motif was also facile. Although the yield was lower than for any other product in the three experimental series, the result compares favorably with yields of benzimidazole derivatives by other synthetic means.[16, 21, 23] Isolation of the tetrahydropyrimidine and benzimidazole products (Figure 14b and 14c, respectively) also allowed isolation of the alternate, bis-amidine products from the reactions (Figure 15). These alternate products were present in very low amounts, and demonstrated the efficiency of our method for formation of the larger motifs. Though

they were not the intended targets of synthesis, one of these alternate bis-amidine products is nonetheless novel (Figure 15a).

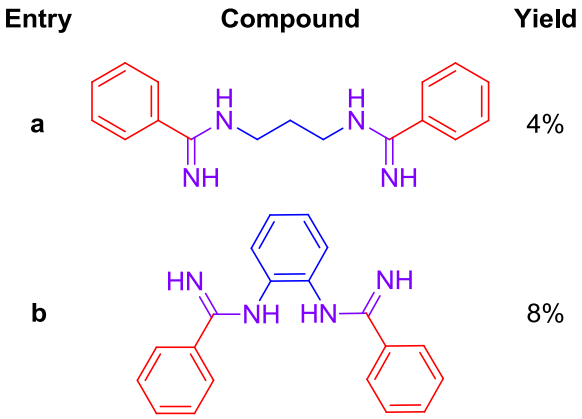


Figure 15: Bis-amidine byproducts

Synthesis of tetrahydropyrimidine and benzimidazole derivatives led to negligible formation of bis-amidine alternate products.

All desired amidine targets in this study were obtainable in yields greater than 40%, often much greater, using 1:1 ratios of starting materials and reaction times of less than 24 hours at room temperature. In addition to demonstrating compatibility with amines and nitriles of varying reactivity, we have shown that generation of bis-amidines and other large, amidine-containing molecular moieties is feasible via our method of amidine synthesis. Furthermore, we have used the method to synthesize six compounds previously undescribed in the scientific literature and characterized them herein. Featuring shorter reaction times, superior yields, better material and time economy, and greater compatibility with a broad range of starting materials, our method of amidine preparation by strong base activation of amines overcomes a number of limitations of existing routes to *N*-substituted aryl amidine synthesis. The method makes accessible a host of new pharmaceutically-relevant species for study against human diseases.

Future Directions

This project successfully developed a new approach to *N*-substituted aryl amidine synthesis and demonstrated its applicability to a range of starting materials for the creation of mono- and bis-amidines, benzimidazoles, and tetrahydropyrimidines. Future work should expand on this foundation, and determine the compatibility of amidine preparation by strong base activation of amines with other starting materials and for the synthesis of different subsets of *N*-substituted amidines.

Further Exploring Starting Material Compatibility

Non-aryl Nitriles

This project studied only the use of aryl nitriles as substrates for amidine synthesis by strong base activation of amines. Preliminary work shows our method may also be suitable for non-aryl nitriles, such as acetonitrile (Figure 16), but further study is necessary to establish compatibility with these starting materials.

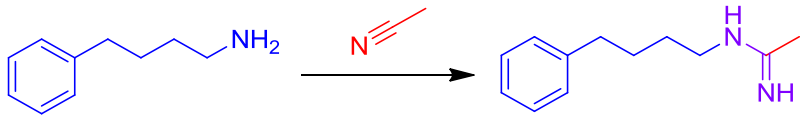


Figure 16: Amidine synthesis from non-aryl nitriles

Doing so may show that our approach overcomes limitations of other synthetic methods that do not tolerate nitriles capable of undergoing a ketamine-enamine tautomerization.

Secondary amines

Secondary amines are more nucleophilic than their primary counterparts. This project studied only primary amines; the facility of amidine synthesis with even deactivated primary aryl amines suggests our method may be compatible with these

more reactive starting materials. To date, no di-substituted amidines have been purified and isolated using our synthetic method. Establishing the broad compatibility of secondary amines with our approach would overcome limitations of synthesis by lanthanide (III) triflates and make accessible a host of unsymmetrical *N*-di-substituted amidines for pharmacological study.

Chemoselectivity

This project demonstrated that our method of synthesis tolerates a competing nucleophilic aromatic substitution site on the nitrile. This chemoselectivity is noteworthy, and suggests amidine formation under the conditions of our method may be favorable to formation of other products. For this reason, it will be important to establish the extent to which other functional group cross-reactivities affect amidine formation by strong base activation of amines. Starting materials containing sites for addition or substitution at a carbonyl group (Figure 17a and 17b, respectively) are of particular interest.

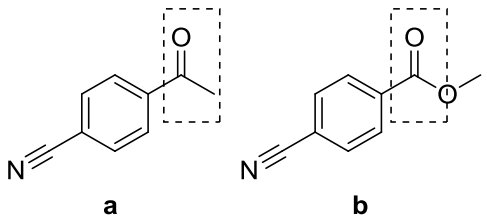


Figure 17: Exploring chemoselectivity of amidine formation

Synthesis of amidines from nitriles with competing reaction sites (dashed box) would further establish the chemoselectivity of our method.

Dinitriles

The compatibility of diamines for the synthesis of large amidine-containing motifs was successfully established in this project; the use of dinitriles remains

unexplored. Bis-amidines of the type described by Wong et al. would be especially facile to make via our method if dinitriles are successfully established as compatible starting materials.

Method Manipulation for Alternate Products

During the course of this project, diamines were successfully used for the generation of both linear bis-amidines and cyclic amidine-containing moieties. Further study is needed to determine whether diamine starting materials that can undergo either transformation can be reliably manipulated towards one or the other product. Specifically, the use of 1, 3-diaminopropane (Figure 11b) and *o*-phenylenediamine (Figure 11c) to generate high yields of the respective bis-amidines in a manner similar to that of *p*-phenylenediamine (Figure 11a) would be of considerable interest.

The generation of bis-amidines via serial activation of amines and subsequent addition of nitriles was highly successful in this project. The ease with which the symmetrical bis-amidine could be generated from the diamine and two equivalents of nitrile suggests unsymmetrical bis-amidines may be similarly generated from serial diamine activation and one equivalent each of different nitriles. Such structures are gaining importance in pharmaceutical chemistry applications, and their accessibility via our method of synthesis would be an important feature to establish.[8, 30]

Properties of Amidines and Amidine Chemistry

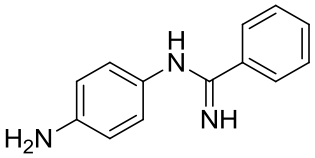
This project established that amidine formation is favored under the given reaction conditions when compared to nucleophilic aromatic substitution (NAS), based on the use of 4-fluorobenzonitrile (Figure 10c) as a substrate. This substrate has also

seen successful use for generation of the NAS product at higher temperatures with a milder base. The underlying mechanisms for the chemoselectivity observed in this project have not been satisfactorily determined, though interplay of kinetics and thermodynamics under the two different reaction conditions is certainly involved. Answering the question of why one product is favored over the other in each reaction may give insight to the relative stability and energy of the two species, and could be approached via decomposition or other studies of the amidine produced in this project.

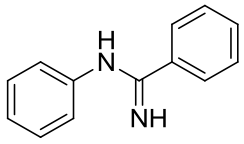
Supporting Information

The following section summarizes all NMR & HRMS data for this project. Procedures used for reactions and characterization have been previously discussed for the layperson in the "Methods and Materials" section, but are summarized here for those interested in the synthetic protocols.

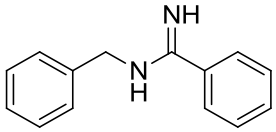
General Procedure: At room temperature, amines are added to 5 mL dry THF under N_2 (g) before addition of n-butyllithium. This is stirred for 15 minutes before addition of nitrile in 1 mL THF. In the case of bis-amidines and cyclic amidines, a second equivalent of n-butyllithium and/or nitrile are added after 1 h in the same manner as above. Reaction is subsequently stirred for 24 h, then quenched with a solution of 1 mL acetyl chloride in 9 mL EtOH.



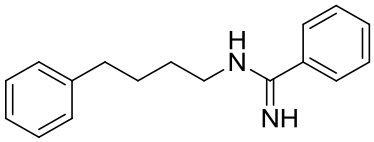
Mono-amidine 12a: Amine **9a** (109 mg, 1.0 mmol) was reacted with *n*-butyllithium (1.2 mmol) and benzonitrile (0.12 mL, 1.2 mmol) according to general procedure. Crude mixture precipitated from 200 mL Et_2O and recrystallized from 10% HCl (aq) to give the HCl salt of **12a** (209 mg, 84%) as a red solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.79 (s, 1H), 9.96 (s, 1H), 9.30 (s, 1H), 7.97 (d, J = 7.0 Hz, 2H), 7.80 (t, J = 6.3 Hz, 1H), 7.70-7.66 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.46, 135.49, 134.31, 129.39 (2), 129.36, 128.98, 128.73, 127.17. HRMS (TOF MS ES+) calculated for $C_{13}H_{14}N_3^+$ [MH^+] 212.1188, found 212.1184.



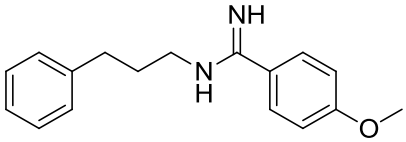
Mono-amidine 12b: Amine **9b** (0.09 mL, 1.0 mmol) was reacted with *n*-butyllithium (1.0 mmol) and benzonitrile (0.10 mL, 1.0 mmol) according to general procedure. Crude mixture precipitated from 200 mL Et_2O and lyophilized from 1M HCl (aq) to give the HCl salt of **12b** (203 mg, 87%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, J = 7.0 Hz, 2H), 7.51-7.44 (m, 4H), 7.33 (t, J = 7.7 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 7.7 Hz, 2H), 6.24 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.69, 135.24, 133.57, 129.88, 128.84, 128.81 (2), 128.04, 125.34. HRMS (TOF MS ES+) calculated for $C_{13}H_{13}N_2^+$ [MH^+] 197.1079, found 197.1141.



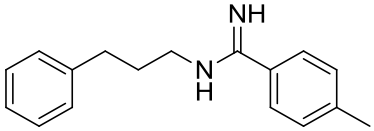
Mono-amidine 12c: Amine **9c** (0.11 mL, 1.0 mmol) was reacted with *n*-butyllithium (1.3 mmol) and benzonitrile (0.12 mL, 1.2 mmol) according to general procedure. Crude mixture precipitated from 200 mL Et_2O before purification by flash chromatography on C18 silica gel. Lyophilized to give the HCl salt of **12c** (182 mg, 73%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.45 (s, 1H), 9.69 (s, 1H), 9.45 (s, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.72 (d, J = 6.7 Hz, 1H), 7.61 (t, J = 6.0 Hz, 2H), 7.48 (d, J = 5.7 Hz, 2H), 7.42-7.34 (m, 3H), 4.74 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.06, 135.59, 133.34, 128.88 (2), 128.58, 128.25, 127.72, 127.67, 45.44. HRMS (TOF MS ES+) calculated for $C_{14}H_{15}N_2^+$ [MH^+] 211.1235, found 211.1236.



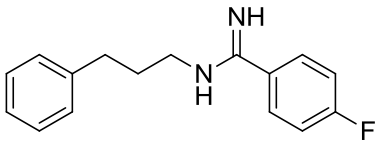
Mono-amidine 12d: Amine **9d** (0.16 mL, 1.0 mmol) was reacted with *n*-butyllithium (1.0 mmol) and benzonitrile (0.10 mL, 1.0 mmol) according to general procedure. Crude mixture purified by flash chromatography on silica gel. Lyophilized to give the HCl salt of **12d** (253 mg, 88%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.55 (s, 1H), 8.05 (s, 1H), 6.94-6.86 (m, 3H), 6.82-6.76 (m, 2H), 6.49-6.33 (m, 5H), 2.68-2.62 (m, 2H), 1.93-1.85 (m, 2H), 1.00-0.93 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.24, 142.35, 133.62, 129.50, 129.30, 128.78, 128.74, 128.66, 126.21, 42.94, 35.13, 28.54, 27.48. HRMS (TOF MS ES+) calculated for $C_{17}H_{21}N_2^+$ [MH^+] 253.1705, found 253.1714.



Mono-amidine 13a: 3-phenylpropylamine (0.14 mL, 0.98 mmol) was reacted with *n*-butyllithium (1.2 mmol) and nitrile **10a** (134 mg, 1.0 mmol) according to general procedure. Crude mixture concentrated and recrystallized from 10% HCl (aq) to give the HCl salt of **13a** (159 mg, 53%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.72 (s, 1H), 9.38 (s, 1H), 9.05 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.33-7.18 (m, 5H), 7.14 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.44 (q, J = 6.7 Hz, 2H), 2.70 (t, J = 7.7 Hz, 2H), 1.95 (p, J = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.09, 162.20, 141.20, 130.17, 128.32, 125.89, 120.66, 114.16, 55.70, 42.25, 32.27, 29.15. HRMS (TOF MS ES+) calculated for $C_{17}H_{21}N_2O^+$ [MH^+] 269.1654, found 269.1647.

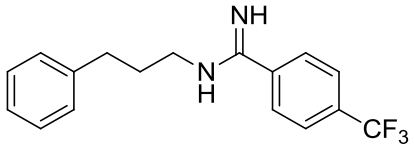


Mono-amidine 13b: 3-phenylpropylamine (0.14 mL, 0.98 mmol) was reacted with *n*-butyllithium (1.2 mmol) and nitrile **10b** (130 mg, 1.1 mmol) according to general procedure. Crude mixture precipitated from 200 mL Et_2O and collected by filter to give the HCl salt of **13b** (205 mg, 72%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.48 (s, 1H), 9.20 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.32-7.17 (m, 5H), 3.46 (q, *J* = 6.7 Hz, 2H), 2.70 (t, *J* = 7.9 Hz, 2H), 2.40 (s, 3H), 1.96 (p, *J* = 7.1 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.76, 143.63, 141.20, 129.30, 128.33, 128.30, 128.14, 126.07, 125.90, 42.30, 32.26, 29.11, 21.03. HRMS (TOF MS ES+) calculated for $C_{17}H_{21}N_2^+$ [MH^+] 253.1705, found 253.1700.

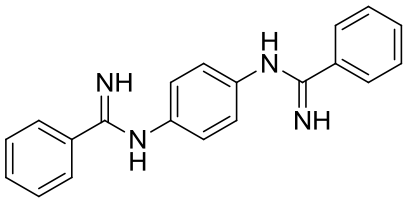


Mono-amidine 13c: 3-phenylpropylamine (0.14 mL, 0.98 mmol) was reacted with *n*-butyllithium (1.0 mmol) and nitrile **10c** (121 mg, 1.0 mmol) according to general procedure. Crude mixture precipitated from 200 mL Et_2O before purification by flash chromatography on C18 silica gel. Lyophilized from 1M HCl (aq) to give the HCl salt of **13c** (191 mg, 66%) as an off-white foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.99 (s, 1H), 9.60 (s, 1H), 9.31 (s, 1H), 7.90-7.85 (m, 2H), 7.50-7.44 (m, 2H), 7.33-7.17 (m, 5H), 3.46 (q, *J* = 6.8 Hz, 2H), 2.70 (t, *J* = 7.8 Hz, 2H), 1.95 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.77 (d, *J* = 251.3 Hz), 161.94, 141.20, 131.22 (d, *J* = 9.4 Hz), 128.32, 128.31, 125.88, 125.45 (d, *J* = 2.9 Hz), 115.89 (d, *J* = 22.3 Hz), 42.42,

32.25, 29.08. HRMS (TOF MS ES+) calculated for $C_{16}H_{18}FN_2^+$ [MH^+] 257.1454, found 257.1453.

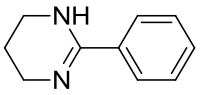


Mono-amidine 13d: 3-phenylpropylamine (0.14 mL, 0.98 mmol) was reacted with *n*-butyllithium (1.2 mmol) and nitrile **10d** (234 mg, 1.4 mmol) according to general procedure. Crude mixture precipitated from 200 mL Et_2O before purification by flash chromatography on C18 silica gel. Lyophilized from 10% HCl (aq) to give the HCl salt of **13d** (240 mg, 71%) as a near-colorless glass: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.87 (s, 1H), 9.63 (s, 1H), 8.01 (d, *J* = 6.3 Hz, 2H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.29-7.27 (m, 4H), 7.19 (d, *J* = 7.1 Hz, 1H), 3.52 (q, *J* = 5.5 Hz, 2H), 2.72 (t, *J* = 7.1 Hz, 2H), 1.97 (p, *J* = 5.9 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.83, 141.27, 132.91, 132.58 (q, *J* = 32.3 Hz), 129.57, 128.32, 125.86, 125.55 (q, *J* = 3.06 Hz), 123.56 (q, *J* = 272.4 Hz), 109.49, 42.59, 32.27, 29.13. HRMS (TOF MS ES+) calculated for $C_{17}H_{18}N_2F_3^+$ [MH^+] 307.1422, found 307.1419.

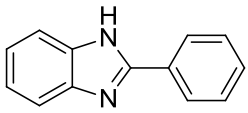


Bis-amidine 14a: Amine **11a** (120 mg, 1.1 mmol) was reacted with *n*-butyllithium (1.3 mmol) and benzonitrile (0.12 mL, 1.2 mmol) for 1 h. Second equivalents of *n*-butyllithium (1.3 mmol) and benzonitrile (0.12 mL, 1.2 mmol) added similarly according to general procedure. Crude mixture precipitated from 200 mL Et_2O and

collected by filter to give the HCl salt of **14a** (364 mg, 85%) as a pink solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.85 (br, 1H), 9.66 (br, 3H), 7.98 (d, J = 6.9 Hz, 4H), 7.78 (t, J = 6.8, 2H), 7.69-7.61 (m, 8H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.96, 136.06, 134.08, 129.32, 129.08, 128.62, 109.97. HRMS (TOF MS ES+) calculated for $C_{20}H_{19}N_4^+$ [MH^+] 315.1610, found 315.1624.

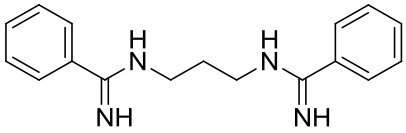


Tetrahydropyrimidine 14b: Amine **11b** (0.08 mL, 0.96 mmol) was reacted with *n*-butyllithium (1.3 mmol) and benzonitrile (0.10, 1.0 mmol) for 1 h. Second equivalent of *n*-butyllithium (1.3 mmol) added similarly according to general procedure. Crude mixture precipitated from 200 mL Et_2O and purified by flash chromatography on C18 silica gel. Major component free-based with 10M NaOH (aq) before separation with EtoAc. Organic fraction concentrated and lyophilized from 10% HCl (aq) to give the HCl salt of **14b** (147 mg, 87%) as a glassy oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.10 (s, 1H), 9.62 (s, 1H), 9.50 (s, 1H) 7.84-7.58 (m, 5H), 3.48 (t, J = 4.6 Hz, 4H) 1.97 (p, J = 5.2 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 133.65, 129.46, 129.33, 128.73, 128.10, 39.22, 18.13. HRMS (TOF MS ES+) calculated for $C_{10}H_{13}N_2^+$ [MH^+] 161.1079, found 161.1072.

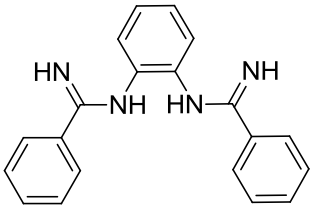


Benzimidazole 14c: Amine **11c** (114 mg, 1.1 mmol) was reacted with *n*-butyllithium (1.3 mmol) benzonitrile (0.12 mL, 1.2 mmol) for 1h. Second equivalent of *n*-butyllithium (1.3 mmol) added similarly according to general procedure. Crude mixture

precipitated from 200 mL Et_2O and purified by flash chromatography on C18 silica gel. **14c** (89 mg, 42%) was isolated as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (d, J = 3.3 Hz, 2H), 7.80 (dd, J = 3.2 Hz, 6.0 Hz, 2H), 7.70 (m, 3H) 7.48 (dd, J = 3.1 Hz, 6.0 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.88, 134.44, 132.85, 129.92, 128.14, 125.61, 125.35, 114.80. HRMS (TOF MS ES+) calculated for $C_{13}H_{11}N_2^+$ [MH^+] 195.0922, found 195.0920.



Bis-amidine 15a: Amine **11b** (0.08 mL, 0.96 mmol) was reacted with *n*-butyllithium (1.3 mmol) and benzonitrile (0.10, 1.0 mmol) for 1 h. Second equivalent of *n*-butyllithium (1.3 mmol) added similarly according to general procedure. Crude mixture precipitated from 200 mL Et_2O and purified by flash chromatography on C18 silica gel to give the HCl salt of **15a** (13 mg, 4%) as an off-yellow oil: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 2H), 9.68 (s, 2H), 9.60 (s, 2H), 7.86 (d, J = 7.9 Hz, 4H), 7.71 (t, J = 7.4 Hz, 2H), 7.59 (t, J = 7.7 Hz, 4H), 3.66 (t, J = 6.3 Hz, 4H), 2.05 (p, J = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.23, 133.70, 129.31, 129.28, 128.75, 40.52, 26.16. HRMS (TOF MS ES+) calculated for $C_{17}H_{21}N_4^+$ [MH^+] 281.1766, found 281.1756.



Bis-amidine 15b: Amine **11c** (114 mg, 1.1 mmol) was reacted with *n*-butyllithium (1.3 mmol) benzonitrile (0.12 mL, 1.2 mmol) for 1h. Second equivalent of *n*-butyllithium (1.3 mmol) added similarly according to general procedure. Crude mixture precipitated from 200 mL Et_2O and purified by flash chromatography on C18 silica gel. **15b** (26 mg, 8%) was isolated as an off-white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (d, J = 6.4 Hz, 2H), 7.85 (d, J = 7.5 Hz, 2H), 7.75-7.70 (m, 3H), 7.65-7.58 (m, 5H), 7.36 (dd, J = 3.1 Hz, 5.9 Hz, 2H). Residual NH_3 (2 equiv.) detected: δ 7.41 (s, 2H), 7.31 (s, 2H), 7.20 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 133.83, 132.69, 131.66, 129.97, 129.68, 127.57, 124.04, 115.14. HRMS (TOF MS ES+) calculated for $C_{20}H_{19}N_4^+$ [MH^+] 315.1510, found 315.1513.

Glossary

The following terms may not be readily familiar to the layperson and so have been defined, to the extent relevant to this project, here.

Acid(s): A substance that can either donate/release a **proton**, generally in the form of an H^+ ion (hydrogen atom nucleus), or accept/recruit a pair of **electrons** [Lewis acids]. Opposite to, and capable of neutralizing, a **base**.

Alkyl: Describes a structure consisting primarily of carbon and hydrogen atoms, and with only single bonds between carbon atoms of the group.

Amine(s): A **functional group** consisting of a nitrogen atom connected only by single bonds to the remainder of the structure. Examples of amine types and nomenclature are shown in Figure 18.

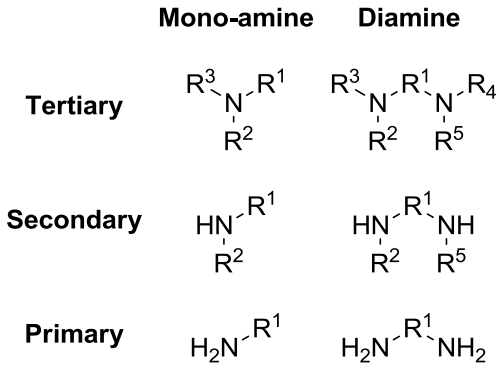


Figure 18: Amine nomenclature

Amines are subject to similar nomenclature as that described for amidines in the "Background" section of this work. The prefixes mono-, di-, tri-, etc. indicate the number of amine groups, while the degree (primary, secondary, tertiary) indicate the number of substituents (non-hydrogen atoms) bonded to the amine.

Analgesic: A substance that relieves pain, often also inflammation.

Anhydrous: Devoid of water.

Anthelminthic: A substance that expels helminthes (large, multi-cellular parasites visible to the naked eye) without adversely affecting the host.

Aryl ring: A **functional group** composed of six carbons, in a ring formation, that is unusually stable in terms of **kinetics**. Species with key **functional groups** appended to the aryl ring are often referred to as "aryl [group name]s".

Base(s): A substance that can accept a **proton**, generally in the form of an H^+ ion (hydrogen atom nucleus), or donate/release a pair of **electrons** [Lewis bases]. Opposite to, and capable of neutralizing, an **acid**.

Benzylic: Describes a structure connected to an **aryl ring** with a single intervening carbon (and its associated hydrogen atoms).

Carbanion: A negatively charged species where a carbon atom bears the negative charge/lone pair of electrons.

Carbonyl group: A **functional group** composed of a single carbon atom double bonded to a single oxygen atom.

Chemoselectivity: The preferential occurrence of one reaction over other possible reactions. Generally results in the formation of a particular product(s) rather than any other(s).

Condensation reaction: A reaction in which water (one oxygen atom and two hydrogen atoms) is effectively generated upon the combining of the starting materials to give the structure of the product(s).

Cross-reactivity: The propensity for a species to react with other **functional groups** in a reaction to create products that were not the intended targets of synthesis.

Deprotonate(d): The process or action of removing a **proton**, often in the form of an H^+ ion (hydrogen atom nucleus), usually by a **base**.

Diamine(s): See **Amine(s)**.

Dinitrile(s): See **Nitrile(s)**.

Electron(s): One of the fundamental particles of matter, an electron has a negative charge. Sharing of electrons constitutes a chemical bond between atoms, and most chemistry can be defined fundamentally as a study of electrons and the elements that share them.

Electron-withdrawing group(s): Any **functional group** that effectively reduces the electron density available to the remainder of the molecular structure to which it is attached.

Electrophilic: The state of having a high affinity for electrons, usually in the form of reactivity towards species that are negatively charged or can otherwise provide electron density to the specie(s) in question. Opposite of **nucleophilic**. Describes a chemical species that accepts an electron pair to formation of a chemical bond during a reaction.

Functionalization: The process of adding **functional group(s)** to a structure or specie.

Functional group(s): In **organic chemistry**, molecule structural motifs usually composed of a few elements and specific number(s)/composition(s) of bonds that share similar properties (reactivity, acidity/basicity, etc.).

Kinetics: The branch of chemistry related to the study of rates of chemical processes.

Lewis acid: See **Acid(s)**.

Lyophilization: Akin to freeze-drying, a process by which water vapor is removed from a sample using a high vacuum at extremely low temperature(s).

Nitriles: A **functional group** consisting of a carbon atom connected by a triple bond to a single nitrogen atom. Nitriles are subject to similar nomenclature as that described for amidines in the "Background" section of this work. The prefixes mono-, di-, tri-, etc. indicate the number of nitrile groups in a given structure. See Figure 19 for additional clarification.

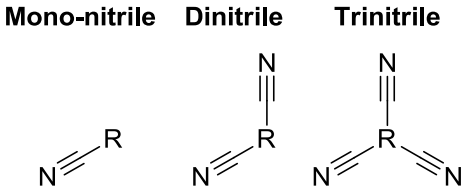


Figure 19: Nitrile nomenclature

This project examined only the use of mono-nitriles (the prefix mono- is often omitted by convention). Use of di- and tri- nitriles may be of importance in the future.

Nucleic acids: Biological molecules, such as DNA and RNA, which encode the genome and provide the instructions for proper cell function. May also refer to their substituent molecular modules.

Nucleophilic: The state of having a high affinity for nuclei/protons, usually in the form of reactivity towards species that are positively charged or can otherwise accept electron density from the specie(s) in question. Opposite of **electrophilic**. Describes a chemical species that donates an electron pair to the formation of a chemical bond during a reaction.

Nucleophilic aromatic substitution: A chemical reaction in which a **nucleophilic** species replaces an **electron-withdrawing group** on an **aryl ring**.

Organic chemistry: The study of compounds composed primarily of carbon, hydrogen, and sometimes oxygen and nitrogen, their reactions and properties.

Proton: One of the fundamental particles of matter, a proton has a positive charge and is found in the nuclei of atoms. A hydrogen atom nucleus is the simplest nucleus, and consists of a single proton.

Protonate(d): The process or action of adding a **proton**, often in the form of an H^+ ion (hydrogen atom nucleus), usually by an **acid**.

Recrystallization: The process of inducing the formation of crystals, molecularly-arranged clusters of the same compound, from a solution containing the compound to be (re)crystallized. The cooking of rock candy is a household form of recrystallization, in this case of sugar.

Secondary amine(s): See **Amines**.

Serine protease(s): Any of a family of proteins that use a serine residue to function.

Silica: SiO_2, the same substance of which glass and sand are composed. In this project, it is used as the solid phase in chromatographic purification.

Strong base: In the context of this project, *n*-butyllithium, a **base** of unusually high strength for which the process of becoming **protonated** is so favorable it releases enough energy to spontaneously combust on contact with air or water.

Synthetic efficiency: The extent to which a reaction converts starting materials to desired products, as measured by the amount of product obtained from a reaction compared to the maximum amount producible by the same reaction. Expressed as a percentage (of maximum products obtainable).

Thermodynamics: The branch of chemistry related to the study of the energy of chemical processes.

Transition element: Any of the elements with atomic numbers 21-30, 39-48, 57-80, or 89-112.

Trimethylsilyl: A **functional group** of the structure depicted in Figure 20.

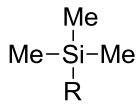


Figure 20: Structure of the trimethylsilyl group

TMS groups consist of a silicon atom bonded to three methyl groups. TMS groups are easily removed in organic synthesis; this property facilitates the preparation of unsubstituted amidines in several literature syntheses (see p. 9)

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