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## Properties, Reactivity and Applications

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ISBN 978-3-030-43480-9 ISBN 978-3-030-43481-6 (eBook)
https://doi.org/10.1007/978-3-030-43481-6

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# Preface

The authors dedicate this work to Rolf Huisgen and his many coworkers, the architects of a tremendous portion of the 1,3-dipole chemistry in use today.

We also wish to clarify a handful of technical details relating to the construction of this manuscript. Firstly, all reported products of 1,3-dipolar cycloaddition reactions afford a single or extremely dominant regioisomer unless otherwise indicated.

Additionally, the literature concerning NIs is dominated by 1,3-dipolar cycloadditions with alkenes, and this may appear disproportionate relative to the page allocation for different NI reaction partners within the *Reactivity* section of this book. We have taken this decision for two reasons. Firstly, the majority of examples of NI-alkene cycloadditions not reported herein apply this reaction as a means to an end and is not the primary focus of the manuscript. All relevant articles that in some manner further the understanding of, or expand the application scope of, the NI-alkene cycloaddition have been included within this book, along with other selected examples. Secondly, the principal objective of the *Reactivity* section of this work is to provide a complete and balanced overview of all potential reaction partners. A vast excess of NI-alkene cycloaddition methodology would only dilute the impact and compromise the structuring of this section.

This book is intended to provide complete, authoritative coverage of the literature up to May 2019 (inclusive). While a handful of citations after this date are included, the authors must stress that it is possible that some publications after this time may have been overlooked due to the preparation of the manuscript taking place during this period.

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# Abstract

A highly reactive member of the nitrilium betaine 1,3-dipole family, the nitrile imine is a versatile species with a wide array of applications ranging from chemical synthesis to biorthogonal ligation and materials chemistry. The promiscuous reactivity of the dipole with a range of nucleophiles, in addition to more conventional dipolarophiles, affords the nitrile imine a unique set of properties with exceptional synthetic utility. This manuscript aims to provide a comprehensive overview of the nitrile imine 1,3-dipole, from its initial discovery in 1959, through to the most recent publications as of June 2019. Topics covered include the core properties of the dipole and the different methods of synthesis available to chemists. Particular attention is paid to the diverse reactivity profile of the nitrile imine and its numerous applications in a diverse range of fields.

# Contents

# About the Authors

**Craig Jamieson** earned his B.Sc. (Hons) in Chemistry at the University of Glasgow in 1996. His Ph.D. studies were carried out under the direction of Prof. R. Ramage at the University of Edinburgh (1999). Following postdoctoral research under the supervision of Prof. S. V. Ley at the University of Cambridge, in 2001 he was appointed as Principal Scientist in GlaxoSmithKline's Discovery Medicinal Chemistry group working on a range of exploratory medicinal chemistry programmes. In 2004, Dr. Jamieson joined Organon Laboratories (later Merck Research Labs) as a Group Leader in the Medicinal Chemistry Department, with responsibility for the hit to clinical candidate optimisation. In August 2010, he was appointed as John Anderson Research Lecturer in Chemical Biology, based in the Department of Pure and Applied Chemistry at the University of Strathclyde.

**Keith Livingstone** completed his M.Chem. in Chemistry with Drug Discovery at the University of Strathclyde (2016) under the supervision of Dr. Craig Jamieson. Keith remained at Strathclyde and is currently in the final year of his doctoral studies with Dr. Jamieson, which have also included two short research secondments at GlaxoSmithKline Medicines Research Centre, Stevenage, and at Westfälische Wilhelms—Universität Münster with Prof. Ryan Gilmour.

# Chapter 1
# Nitrile Imines and Their Properties

**Abstract** This chapter introduces the nitrile imine 1,3-dipole, examining the history behind its discovery and the core spectroscopic characteristics associated with the species. The different resonance forms available to nitrile imines can often complicate their characterisation, however appropriate interrogation of data such as UV-Vis, IR and NMR spectra may elucidate the core properties of the dipole. Substitution on either terminus of this typically highly reactive intermediate can also improve stability, enabling the isolation of some nitrile imines at room temperature.

**Keywords** Nitrile imine · 1,3-dipole · Spectroscopy · Properties · Isolation

## 1.1 History

The generation of nitrile imines (NIs) can be traced back to the beginning of the twentieth century, although these reports lacked both characterisation and application of the highly reactive species. The first synthetically tractable report came from Huisgen in 1959 [1]. This initial study was remarkably comprehensive, documenting multiple approaches towards the generation of the NI and detailing its reactivity with a number of dipolarophiles and nucleophiles. Huisgen dominated the area for much of the next decade and provided invaluable insights into the reactivity, kinetics and chemoselectivity of NIs through a number of publications [1–18].

Interest in the applications of NIs was more sparse over the next few decades, with the majority of publications focussing instead on the mechanism of their formation, or their reactivity with different substrates. Recently, however, NI chemistry has enjoyed a renaissance throughout the literature, with a raft of applications identified in the synthesis of APIs, bioorthogonal conjugation, and materials chemistry, over the past fifteen years [19–21].

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C. Jamieson and K. Livingstone, *The Nitrile Imine 1,3-Dipole*,
https://doi.org/10.1007/978-3-030-43481-6_1

## 1.2 Resonance Forms

NIs are members of the nitrillium betaine family of 1,3-dipoles, which possess the general formula outlined in Fig. 1.1 [22]. These are isoelectronic with the allyl anion, with 4π electrons shared across three atoms. The inherent reactivity of 1,3-dipoles comes from the incomplete octet of the neutral terminus, which gives rise to a number of potential resonance forms. The contribution of each of these canonical forms is highly important in governing the reactivity of the species.

Two resonance forms can be viewed as the dominant contributors to NI structure: the propargylic and allenic forms (Fig. 1.2). From a geometric perspective, the propargylic structure can be described as planar (with respect to the N–C–R bond axis), while the allenic form is slightly "bent" [23]. NIs are often referred to as "floppy" molecules, with a low interconversion energy barrier between the two isomers [23–25].

Which of these two resonance forms predominates depends significantly on the substituents on both termini of the NI [26]. One of the most important factors is the electronegativity of the terminal nitrogen atom. Increased electronegativity at the nitrogen tends towards the linear, propargylic structure, forming a more electrophilic dipole with a low-lying LUMO, and vice versa in the case of the allenic form [27, 28].

Significant effort has been invested into the understanding of the dominant resonance form of formyl NI, the simplest member of the family. Prior to the 1990s, a number of theoretical reports had indicated that the propargylic form was preferred

**Fig. 1.1** The general structure of the nitrillium betaines

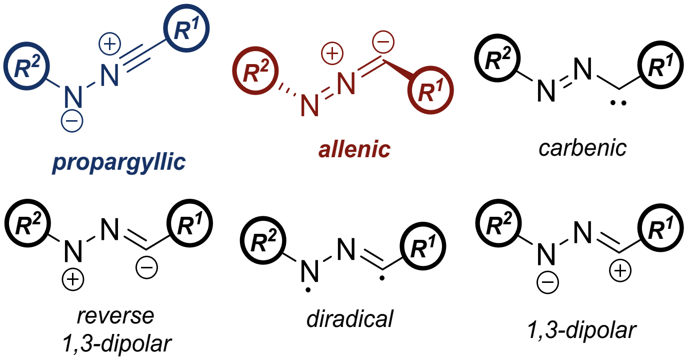
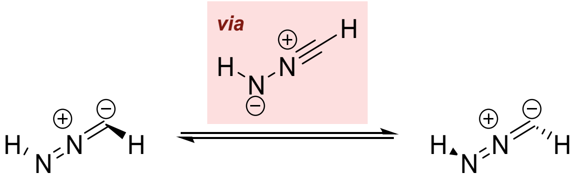


**Fig. 1.2** The six potential resonance forms of NIs

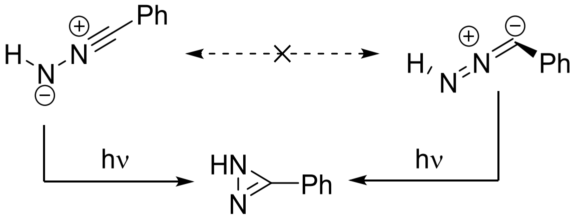
[29–34]. However, as computational power progressed and higher levels of theory were applied, it was later determined that formyl NI existed as the allenic structure almost exclusively, with the propargylic form existing only as a transition state between two stereoisomers of the bent species (Scheme 1.1) [24, 25, 35–39].

Substitution on either terminus of the NI makes the situation more complex, although the original findings still hold true: NIs may have mostly allenic or propargylic structures, largely depending on the electronic properties of their substituents. Multiple examples of both allenic [40–42] and propargylic [28, 43–45] NIs exist in the literature. In the case of 5-phenyl NI, the propargylic and allenic forms have been demonstrated to exist as two independent energy minima (Scheme 1.2) [46]. These two structures therefore cannot be considered different resonance forms but are instead an example of bond-shift isomers, a relationship that may hypothetically be applicable to a number of other NI species [47].

More recently, attention has turned to the importance of the contribution of the carbenic resonance form of NIs. Computational studies have indicated that substitution of the *C*-terminus of the NI with a heteroatom such as nitrogen or oxygen could increase the carbenic character to up to 20% of the overall resonance contribution [48, 49]. This has been partially confirmed experimentally, with 5-amino NI shown via IR spectroscopy to exhibit the lowest C–N bond order of any NI ever recorded [49].



**Scheme 1.1** The hypothesised ground configurations of formyl NI



**Scheme 1.2** Both isomers of 5-phenyl NI are detectable as separate species, and react at different rates to give the same product

## 1.3 Spectroscopy and Isolation

A number of spectroscopic techniques have been employed in an effort to suitably characterise NIs. As would perhaps be expected in a nitrillium betaine 1,3-dipole, the inherent reactivity of the species is a major stumbling block in this process.

Following on from their initial application, [1] any preliminary evidence of the existence of an NI intermediate within a reaction profile was indirect, [18] with the first direct detection of an NI reported in 1973, using UV spectrometry at cryogenic temperatures [50].

Multiple approaches towards the spectroscopic characterisation of NIs were reported throughout the 1980s. The UV spectra of diphenyl NI and derivatives were reported independently by both Holm and Heimgartner, employing 12 K matrix isolation and immobilisation using EPA or PVC glass [51–53]. The IR spectra were also disclosed [53]. The palette of diaryl NIs characterised using this technique increased towards the middle of the decade, with over 20 UV and IR spectra reported [54–57]. The utility of this approach was significantly bolstered with the application of "flash" photolysis, enabling the direct capture of the UV spectrum of an NI at room temperature [58, 59].

Other spectroscopic approaches were also developed, principally using high temperature gas phase techniques [60]. Generation of the NI in this way enabled analysis through mass spectrometry, photoelectron spectroscopy, or IR via immobilisation of the NI on a KBr disc [24, 61]. Modern-day advances in IR technology have recently seen the re-emergence of this approach as the most valuable analytical technique in the characterisation of reactive NIs [26, 49, 62].

$^{14}$N NMR has also been shown to be a feasible approach towards NI identification, although a limitation of this technique is that the NI is required to have enhanced stability relative to other spectroscopic approaches [63]. More recently, photocrystallography was also employed as a method of generating crystal structures of diaryl NIs [64]. Formyl NI has also been shown to be detectable, via either gas-phase neutralisation-reionisation mass spectroscopy, or low-temperature IR spectroscopy [36, 37].

### *1.3.1 Ultraviolet*

NI UV spectra are dominated by a large signal around 240–275 nm (heteroatom-substituted NIs) or 370–465 nm (diaryl NIs) [50–54, 56, 58, 59, 61, 65]. This is postulated to originate from a $\pi$-$\pi^*$ transition, with, in the case of diaryl NIs, an extremely large extinction coefficient leading to a very broad signal [58]. Electron-rich species on the *N*-terminus of the NI and electron-deficient species on *C*-terminus will further increase absorption wavelength [58]. The UV spectrum of formyl NI has never been recorded, however it is predicted to have a maximum absorbance of around 230 nm [25].

### 1.3.2 Infra-red

IR spectroscopy is one of the most valuable techniques in determining whether a specific NI will adopt an allenic or propargylic structure, as the most prominent peak of the spectrum corresponds to the C–N antisymmetric stretch, with the stretching frequency increasing with increasing bond order. All NIs with a C–N stretch frequency below 2100 $\mathrm{cm}^{-1}$ are almost entirely allenic (C–N bond order of 2), while those with a stretch frequency above 2200 $\mathrm{cm}^{-1}$ are likely to primarily exist as the propargylic resonance form. Those with a value between 2100 and 2200 $\mathrm{cm}^{-1}$ exhibit both allenic and propargylic character [66].

Most diaryl, or even monoaryl NI species have been shown to possess a predominantly propargylic structure through this technique (C–N stretch typically ranges from 2215 to 2250 $\mathrm{cm}^{-1}$) [53, 55, 57, 61]. The addition of any conjugative functional group onto either of the aromatic rings, electron donating or withdrawing, will lower the bond order of the C–N bond and will lower the stretching frequency accordingly [57]. NIs substituted by heteroatoms typically adopt allenic or mixed resonance forms, with C–N stretch values between 1990 and 2170 $\mathrm{cm}^{-1}$ [26, 43, 45, 48, 49, 66–68]. An IR spectrum of formyl NI has been recorded, with a C–N stretching frequency of 2027 $\mathrm{cm}^{-1}$ [36]. This is in relatively good agreement with the relevant calculated spectral values for this dipole species [25, 36].

### 1.3.3 Nuclear Magnetic Resonance

There has been considerably less focus on the characterisation of NIs by NMR in comparison to IR and UV spectroscopy, likely due to the relatively specialised conditions required to capture an NMR spectrum making the stability of the compound a necessity.

In the specific cases where NI NMR spectra have been examined, $^{13}$C resonances have been observed between 45 and 70 ppm [25, 63]. This is complicated by large $T_1$ values and small $T_2$ values, which can lead to extremely broad and undetectable peaks [63]. $^{14}$N NMR is a viable alternative, which generates a signal for the α-N at around −215 to −170 ppm [63] (Fig. 1.3).

### 1.3.4 Isolation of NI Compounds

While spectroscopic analysis of a multitude of different NI species rapidly became commonplace during the 1980s, the high reactivity of the dipole still prevented isolation. Alternative syntheses of the NI would prove necessary for any further progress to be made in the area.

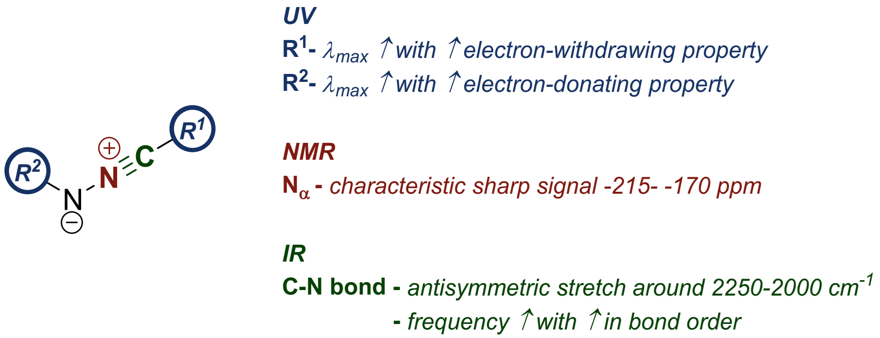
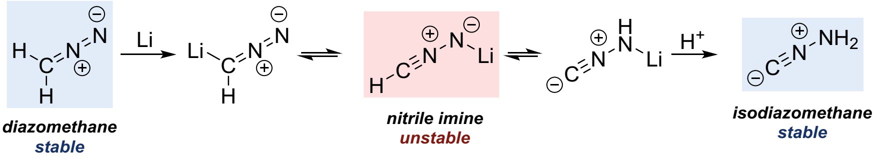


**Fig. 1.3** A summary of the spectroscopic characteristics of NIs

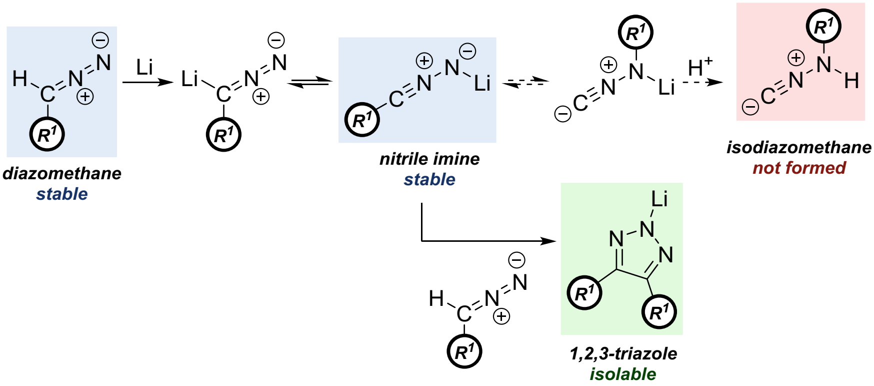
The deprotonation of diazomethane using an alkali metal was first performed by Müller in 1933 [69, 70]. Upon aqueous work-up, an unidentified second product was isolated. This was assigned a cyclic structure, and referred to by Müller as isodiazomethane [71]. Further structural elucidation led to the reassignment of isodiazomethane to the structure of formyl NI, [72–75] however, this was eventually further revised to the correct structure of *N*-aminoisonitrile [76–78]. The mechanism for this isomerisation proceeds via the lithiated formyl NI, which has been shown to be highly unstable in relation to the other two isomers, and exists only as a transition state (Scheme 1.3) [79].

The reactivity of lithiated diazo species changes dramatically upon substitution of the carbon atom of diazomethane [80]. This can be attributed to the stability of the two different NI species involved, where substitution of the formyl NI with even just an additional carbon atom or a trimethylsilane group can substantially stabilise the species [79]. In this way, application of a simple NI generated from this method can function as a reactive intermediate (Scheme 1.4), [81, 82] and even allow low temperature co-crystal structures of lithiated NIs [83].

Due to the comparable stability of these *C*-substituted, lithiated NI species and their lithiated diazo isomers, it was reasoned that treatment of these compounds with an appropriate electrophile may lead to attack on either the *C* or *N* terminus of the diazo/NI functional group. Should this transformation prove chemoselective, it therefore follows that it would be possible to prepare an NI derivative with bulky stabilising *C* and *N* substituents.



**Scheme 1.3** Base-mediated isomerisation of diazomethane

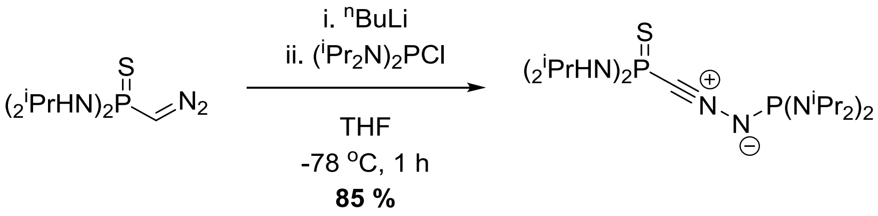


**Scheme 1.4** Base-mediated isomerisation of a substituted diazomethane leads to an NI intermediate

This indeed proved to be the case, with the isolation of the first ever room temperature-stable NI achieved by Bertrand in 1988 (Scheme 1.5) [40, 68]. Bulky substituents were shown to be key in the stabilisation of the compound, and indeed it was later shown that this influence was purely steric in nature, with smaller groups providing either a much more reactive NI or the corresponding diazomethane isomer [84].

The scope of stable NI derivatives was gradually expanded to include NIs bearing silyl [65, 85] and boryl [86] substituents, with a number of combinations of the three possible. Steric bulk was essential in all of these examples, somewhat limiting the scope.

Stannylated diazo compounds were soon found to be a valuable alternative to lithiated diazo compounds. This is due to the greater steric bulk of the $SnMe_3$ functionality relative to the Li cation. This facilitates the presence of a less bulky substituent on the *C*-terminus of the resulting NI, due to the sterically-directing $SnMe_3$ moiety [84]. This procedure was utilised in the synthesis of the first reported example of a room temperature-stable NI with no heteroatomic substituents, again by Bertrand and coworkers, in 1992 (Table 1.1, entry 4) [41]. Using these new stannylated derivatives, the scope of stable NIs was further expanded to include



**Scheme 1.5** The synthesis of the first NI stable at room temperature