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Isonitrile Containing Compounds: an Unexploited Opportunity for Medicinal Chemists?

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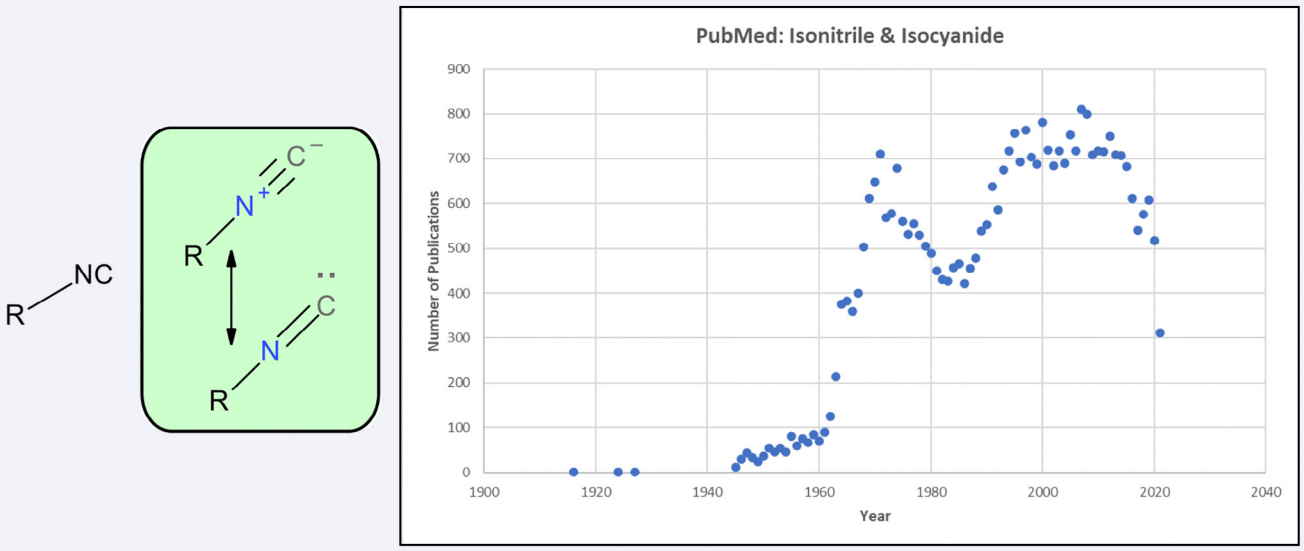
A Brief Introduction to Isonitriles

Isonitriles (or isocyanides) were first described in the mid-19th century and have been the subject of hundreds of papers in the literature over the years (Figure 1). Since interest in the field started to grow more rapidly in about 1960 there have typically been around 550 papers per year which contain a reference to either isonitriles or isocyanides. After a decline in publication numbers in the 1970's, there was a clear resurgence in the area from around 1990. This can potentially be attributed to the evolution and growth of combinatorial chemistry, higher throughput chemistry and compound library synthesis, all of which draw heavily on the synthetic potential of functional groups including isonitriles.

Figure 1. *Pubmed search results, with isonitrile or isocyanide in the title or abstract*



Isonitriles can be synthesised using a range of methodologies and starting materials. These include a the classical method published in 1859 using alkylation of silver cyanide, through dehydration of formamides, and from amines using difluorocarbene. Recent work has sought to facilitate synthetic access to isonitriles and enable preparation of a much more diverse range of examples.

The isonitrile functional group is known for being extremely versatile and is used as a reacting partner in building blocks for a wide range of reactions, foremost amongst these being multi-component reactions such as the Ugi Reaction. Utilisation across important new areas in organic synthesis such as DNA-Encoded Libraries (DEL) have been described recently. Furthermore, reagents such as toluenesulfonylmethyl isocyanide (TosMIC) (CAS# 36635-61-7) have also found considerable utility in heterocycle synthesis (Figure 2). More broadly, the isonitrile group is isoelectronic with CO, and has attracted utility as a ligand in organometallic chemistry. On a practical level some isonitriles require careful handling and have attracted a reputation for having a disagreeable odour, which is well deserved for many lower molecular weight examples. However, as with their mercaptan cousins, the characteristic smell ablates as molecular weight increases and vapour pressure decreases, and handling / containment issues become less of a concern.

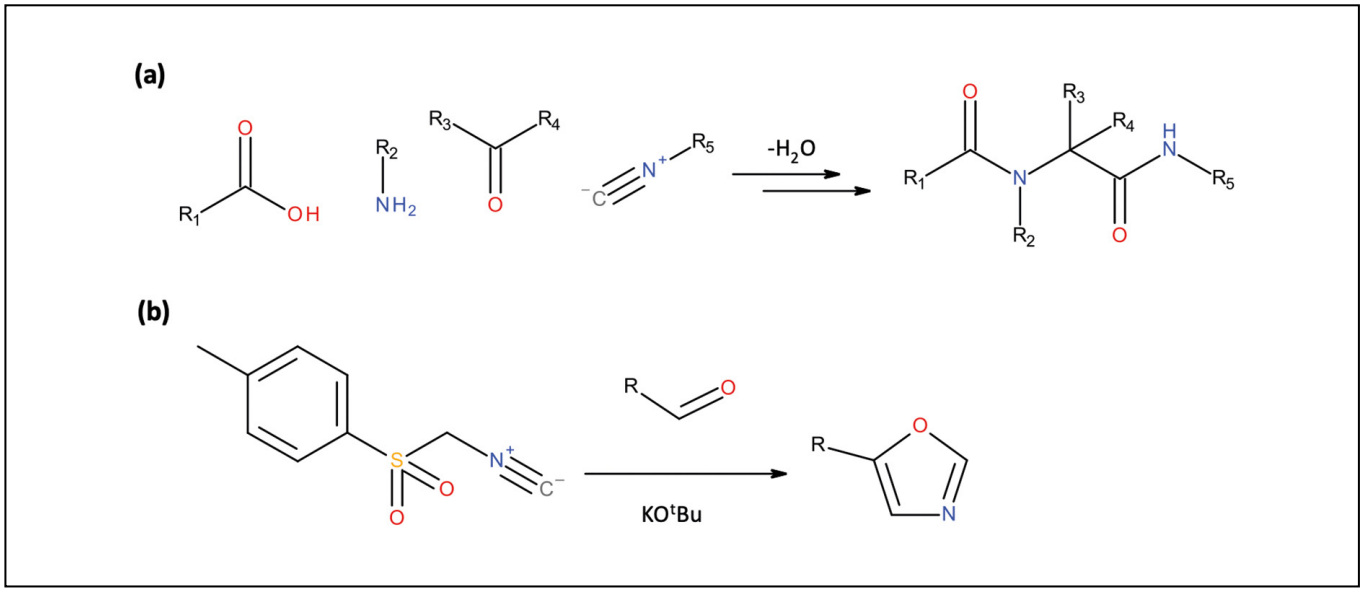


Figure 2. *The Ugi Reaction (a) and toluenesulfonylmethyl isocyanide [TosMIC] synthesis of oxazoles (b)*

Isonitrile containing natural products have been found from a variety of sources, despite the unusual nature of the functional group. The first of these compounds was isolated in 1950, with this number steadily rising over in recent years. Examples from different sources are illustrated in Figure 3.

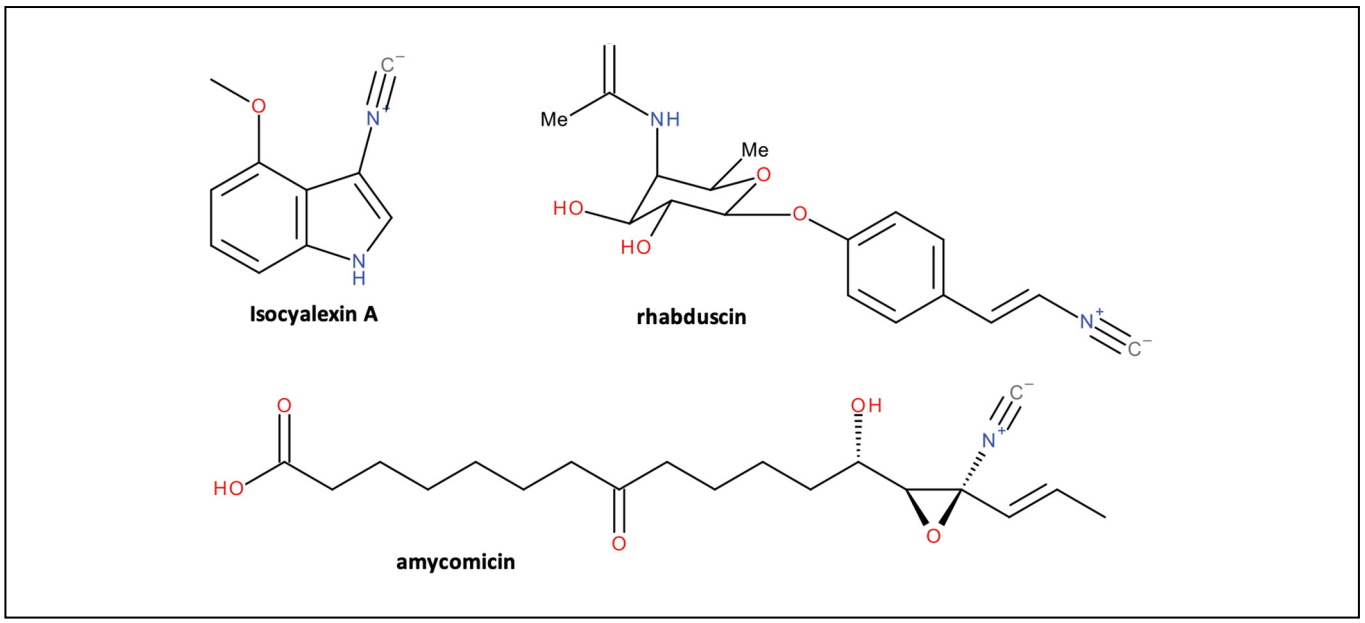


Figure 3. *Isocyalexin A, rhabduscin and amycomicin, representative examples of isonitrile containing natural products*

Isonitriles in Medicinal Chemistry

Despite the high prevalence of isonitriles in the contemporary organic chemistry literature, other than use as synthetic intermediates or building blocks for analogue preparation, medicinal chemists have been slow to utilise this functional group as a structural motif or pharmacophore during hit generation or lead optimisation programs. This may be due to a perception that isonitrile containing compounds are too reactive, are not druglike or have unsuitable properties. It is interesting to note that when simple representative examples are subjected to analysis by commonly used tools including PAINS filters and molecular property calculators, these do not flag isonitrile containing compounds as having non-druglike or problematic characteristics (Figure 4). Moreover, the *in silico* calculated properties of isonitriles are broadly in line with those of other functional groups commonly used in medicinal chemistry.

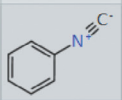
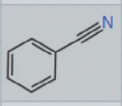
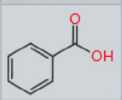
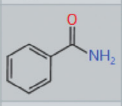
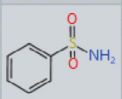
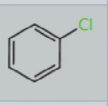
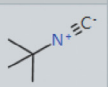
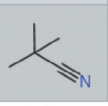
Name	Structure	cLogP	cLogS	H-Acceptors	H-Donors	Polar Surface Area	Druglikeness	Mutagenic	Tumorigenic	Reproductive Effective	Irritant	Nasty Functions
aryl isonitrile		1.4	-2.3	1	0	4.36	-5.97	none	none	none	none	
aryl nitrile		1.5	-2.4	1	0	23.8	-6.05	high	none	none	high	
aryl acid		1.1	-1.6	2	1	37.3	-1.84	high	none	none	high	
aryl amide		0.75	-1.7	2	1	43.1	-0.68	high	none	none	none	
aryl sulfonamide		0.42	-1.5	3	1	68.5	-5.01	none	none	none	none	
aryl chloride		2.3	-2.4	0	0	0	-2.09	high	high	high	none	
alkyl isonitrile		0.87	-1.1	1	0	4.36	-7.77	none	none	none	none	
alkyl nitrile		1.5	-1.7	1	0	23.8	-10.9	none	low	low	none	

Figure 4. *Calculated properties for isonitriles and comparisons to common other functionalities*

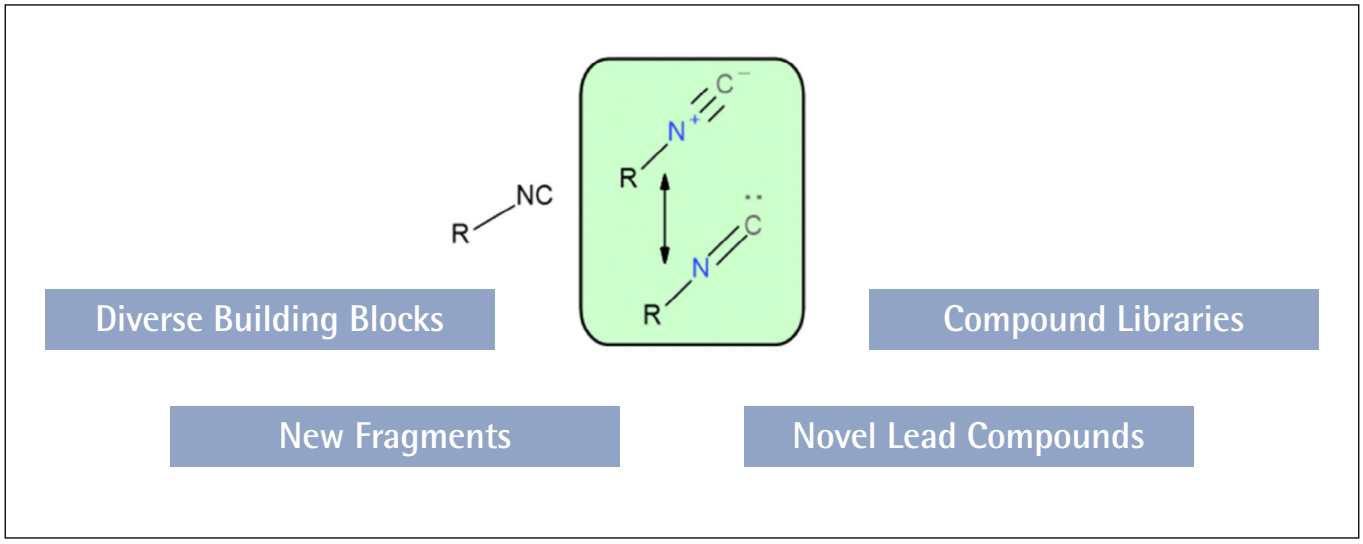
A recent review has highlighted the relative lack of utilisation of isonitriles in medicinal chemistry, and notes that the functionality is unreactive and remains unchanged under common physiological conditions in cells. Also described therein is a detailed overview of the wider characteristics of isonitriles, along with their uses. Of particular interest is the survey of known biological activity profiles of isonitrile containing compounds. These are exemplified with a range of synthetic and naturally occurring derivatives, and include antibacterial, anti-fungal and insecticidal applications, alongside some examples from the oncology and herbicide area. Perhaps the most intriguing possibility for utilisation of isonitriles noted therein is as a novel warhead for metalloenzyme drug targets. At this time there have been few such applications described, with this opportunity not having been widely exploited, the authors attribute this to the perception by medicinal chemists of problems of reactivity or instability.

Another recent publication has also noted this problematic perception, and importantly highlights the paucity of evidence supporting it, in noting there is little or no relevant bioassay data for isonitrile containing compounds in the peer reviewed literature. To start to address this data deficit, the authors selected a small set of representative aryl and alkyl isonitriles and employed them as exemplars to generate baseline data on chemical and metabolic stability under various conditions. The results were intriguing. The resulting data shows that more heavily substituted alkyl groups appeared to confer greater (metabolic) stability on the isonitrile group, and clearly points to opportunities to exploit this in the development of novel lead structures. It is also intriguing to speculate whether aryl isonitriles containing flanking functionality would confer greater stability in a similar manner. Given the low prevalence of isonitriles as exemplified compounds claimed in the patent literature[1] there exists a potential opportunity to rapidly generate novel, non-obvious compounds for a wide variety of therapeutic areas.

1. Using the SureChEMBL database (https://www.surechembl.org/search/), <500 specifically exemplified isonitriles, and <100 specifically exemplified aryl isonitriles were found.

In a similar vein, the use of isonitrile containing start points for medicinal chemistry projects appears not to have been widely considered. Whilst it is possible to purchase a reasonable range of isonitrile containing compounds from various vendors, these often seem to fall within the category of building blocks, rather than being categorised for use as screening compounds (HTS or fragment based drug discovery). Similarly, the synthesis of isonitrile containing compound libraries for fragment or HTS screening is rarely described. Bearing in mind the published stability characteristics, their use in both these applications would appear to be viable and widen the utility of isonitriles beyond their current sole use as building blocks. These could provide new and structurally novel start points for later optimisation into lead molecules.

Additional work is clearly needed to study the characteristics of more highly functionalised isonitrile containing compounds in drug-like space, and to evaluate them in a wider range of assays and test systems representative of typical lead discovery / optimisation projects. This will enable the medicinal chemistry community to better evaluate the strengths and weaknesses of utilising this functional group in their own projects. Overall, the opportunities for isonitrile containing lead molecules appear compelling, and warrants continued review.



Key Organics offers a range of off-the-shelf products available for workers interested in utilising isonitriles. We provide support for academic, biotech and pharma customers in this area through our growing range of isonitrile containing building blocks, precursors for their synthesis and can also offer bespoke compound management services, carefully customised to the requirements of our clients. The highly experienced team at Key routinely undertake synthesis of bespoke or non-commercial building blocks and lead compound(s) on either a custom fee-for-service (FFS) or contract (FTE) basis to support Hit Identification, Hit-to-Lead and Lead Optimisation activities for your discovery program.