



Cite this: *Org. Biomol. Chem.*, 2025, **23**, 7244

Received 25th April 2025,
Accepted 14th July 2025

DOI: 10.1039/d5ob00677e

rsc.li/obc

2-Isocyanoanilines and their mono-Boc-protected derivatives†

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Among the variety of synthetically useful isocyanides, 2-isocyanoanilines have been scarcely reported in the chemical literature, despite the rich chemistry that expectedly could derive from the reactivities of their two functional groups. This is the case not only for the parent compound but also for most of their *N*-monosubstituted derivatives. The reason behind such behavior relies upon their chemical instability, apparently attributable to the presence of the N–H bond. Among these latter species, two *tert*-butyl carbamates are notorious exceptions, as they have been widely utilized in multicomponent reactions but poorly described. This review covers the chemistry of these compounds from a critical perspective, analyzing the causes of the instability of these privileged molecular scaffolds, as well as highlighting the reactivity of their mono-Boc-protected derivatives.

1. Introduction

Isocyanides, also named isonitriles, are highly versatile building blocks in organic synthesis. This versatility stems from the carbene-like reactivity of their divalent carbon atom, enabling them to participate in a wide array of reactions that form both carbon–carbon and carbon–heteroatom bonds. Consequently, isocyanides have been extensively utilized to synthesize a diverse range of molecules.¹

They are exceptionally adaptable compounds, capable of acting as both electrophiles and nucleophiles in different chemical processes. The best-known chemical behavior of isocyanides is their participation in multicomponent reactions.² They are potential carbon monoxide equivalents in certain transformations,³ and their carbene-like character allows them to participate in insertion reactions.⁴ Remarkably, isocyanides are involved in cycloaddition reactions.⁵ This versatility of isocyanides has made them ideal scaffolds in multicomponent reactions, thus occupying a privileged position for obtaining different adducts, highlighting their applications in the preparation of different target heterocycles.^{2e,6} In this scenario, the chemistry of isocyanides has aroused the interest of numerous synthetic chemists, leading to major advances in the research field, including the development of isocyanide-based multicomponent reactions in water⁷ and the employment of these privileged molecules in bioorthogonal chemistry.⁸

Beyond their rich chemistry, the handling of isocyanides turns out to be particularly complicated, mainly because of their instability.⁹ Indeed, these compounds can undergo self-condensation reactions, yielding oligomers and polymers, even at room temperature when stored as solids, liquids or in concentrated solutions.¹⁰

Thus, research focused on the use of these compounds aims to obtain isocyanides with enhanced reactivity while at the same time dealing with their stability. This direction has led to the incorporation of a second functional group into the carbon framework in the vicinity of the isocyanide function, which results in a richer chemistry. Within this rational functionalization design, isocyano-amine-based compounds have emerged as privileged building blocks in different transformations. In the context of our recent interest in isocyanide chemistry,¹¹ 2-isocyanoanilines, **1**, have attracted our attention. In this review, we highlight the chemistry of 2-isocyanoanilines, which are an enigmatic class of isocyano-amines, and their corresponding carbamates.

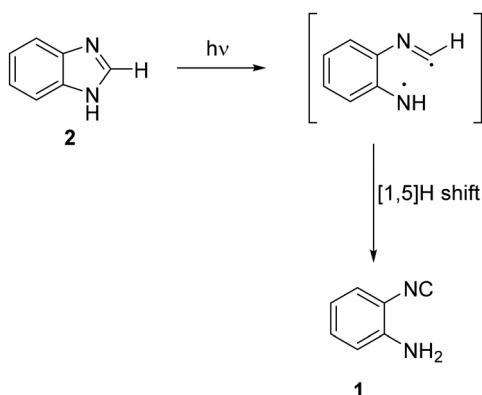
2. 2-Isocyanoanilines

As previously stated, isocyano-amines exhibit enhanced reactivity due to the amino functional group near the isocyanide motif. Among the members of this family of compounds, the 2-isocyanoanilines are the focus of this review, more specifically, the parent compound and its mono- and disubstituted derivatives at the amino group (irrespective of the presence or absence of additional substituents on the aromatic ring). Such species captured our curiosity because they are scarcely reported, most probably due to the *ortho*-disubstitution. Such

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† Dedicated to the memory of Prof. Rafael Pedrosa (1948–2023).



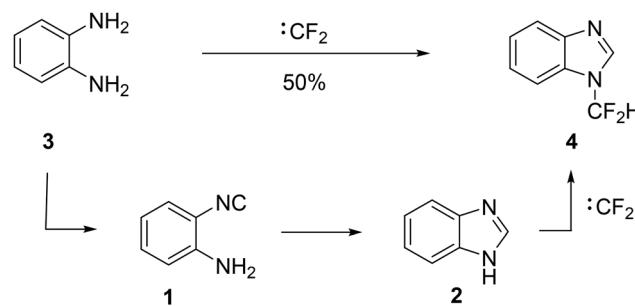
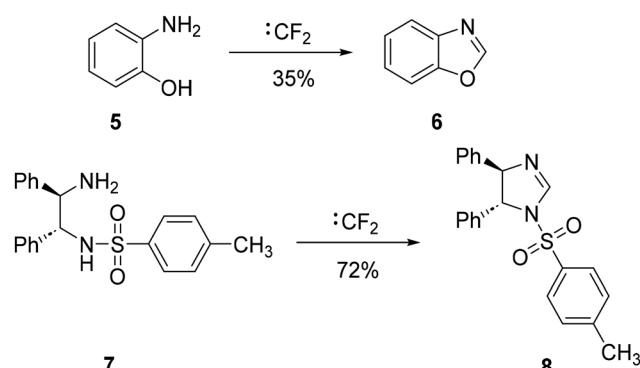


Scheme 1 Synthesis of 2-isocyanoaniline (1).

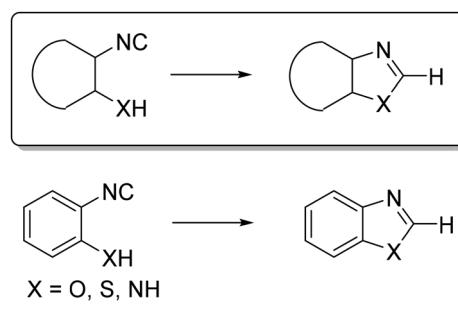
an assumption is based on the following observation: while unsubstituted 3- and 4-isocyanoanilines appeared (at least) in 3 and 30 publications, respectively, in a recent search in SciFinder®, 2-isocyanoaniline **1** has only been reported in one recent publication¹² as one of the products resulting from the photoirradiation of monomeric benzimidazole isolated in a cryogenic argon matrix at 15 K. Its formation is explained as resulting from the ring opening of the imidazole moiety (**2**), coupled with an H-shift from C2 to N1 (Scheme 1). This isocyano-amine was not isolated but only spectroscopically detected.

Apparently, 2-isocyanoaniline **1** is a particularly unstable compound. Thus, while the reaction with chloroform and a strong base (dichlorocarbene synthesis, also known as the Hofmann carblylamine reaction) of *m*- and *p*-phenylenediamines led to the respective isocyano-anilines, the same reaction with an *o*-phenylenediamine (**3**) was unsuccessful in yielding 2-isocyanoaniline **1**.¹³ The presumed instability of 2-isocyanoaniline **1** could also be the reason why 1,2-diisocyanobenzene, a known species, has never been prepared by the above synthetic methodology starting from an *o*-phenylenediamine (**3**), probably because of the rapid consumption of 2-isocyanoaniline **1** formed as the primary product of that process.¹⁴ A recently disclosed new general method for synthesizing isocyanides from the respective primary amines, through a reaction with the *in situ* generated difluorocarbene, sheds light on what types of products derive from the putative 2-isocyanoanilines.¹⁵ In the case of using an *o*-phenylenediamine (**3**) as the substrate, such a reaction led to 1-difluoromethylbenzimidazole (**4**) (Scheme 2). As the authors of that research point out, this latter species probably arises from the cascade isocyanide formation/insertion of the isocyano group into the N–H bond in the initially formed 2-isocyanoaniline (**1**), thus yielding benzimidazole (**2**), which reacted further with a second equivalent of difluorocarbene, inserting into its N–H bond.

Under the same reaction conditions, 2-aminophenol (**5**) yielded benzoxazole (**6**), whereas an ethylenediamine derivative, **7**, with a more flexible backbone, efficiently produced the corresponding dihydroimidazole **8** (Scheme 3).

Scheme 2 Formation of 1-difluoromethylbenzimidazole (**4**).Scheme 3 Synthesis of dihydroimidazole **8**.

In light of these results, it is clear that the reason for the instability of 2-isocyanoanilines (and probably other isocyano-amines) is the rapid intramolecular insertion of the isocyano group into the nearby N–H bond, which precludes their isolation and converts them into benzimidazoles (or other cyclic formamidines). In fact, this was clearly stated by F. E. Hahn, who wrote "... 2-aminophenyl isocyanide is not stable as a free molecule and cyclizes to give benzimidazole" in an article published in 2003,¹⁶ although such an assertion was not supported by a pertinent bibliographic reference. Also, the results in Schemes 2 and 3 indicate that this might be a general behaviour of isocyanides bearing nearby X–H groups, X being an electronegative element or a group such as O, S, and NH (Scheme 4).



Scheme 4 Reactivity of isocyanides bearing X–H groups in the ortho-position.

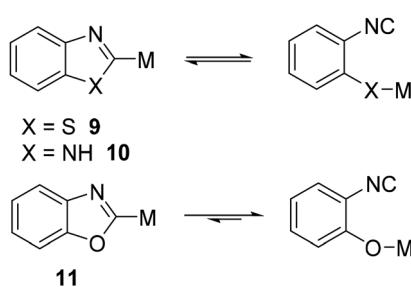
To our knowledge, in the *ortho*-substituted benzene framework, such a conversion has been proved in the case of $X = O$, that is, in 2-isocyanophenol, this process easily occurs to give benzoxazole, either upon standing at room temperature¹⁷ or under photoirradiation.¹⁸ However, in the only report dealing with the thia-analogue $X = S$, 2-isocyanothiophenol, the *in situ* generation of this isocyanide by photolysis of benzothiazole was followed by the formation of tautomers and decyanation species, not returning back to the starting heterocycle.¹⁹ Computational studies of closely related processes, such as the formation of the non-fused analogues oxazole²⁰ and thiazole²¹ from the respective open-chain OH and SH isocyano species, have also been carried out.

In addition, experimental studies on the equilibria between 2-metalled benzothiazole **9** and benzimidazoles **10** with their respective open-chain isocyanide tautomers have also been reported (Scheme 5). In the case of 2-metalled benzoxazole **11**, the equilibrium is completely shifted to the acyclic isomer.²²

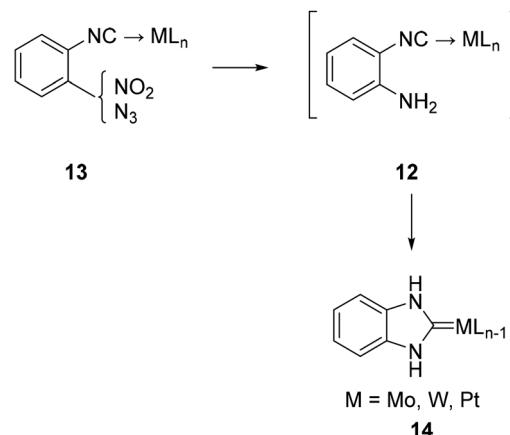
In the present context, the chemistry of metal complexes of 2-isocyananilines **12** is worth a mention here. These species are formed starting from metal phenylisocyanide complexes **13** bearing, in the *ortho*-position to the isocyanato group, a nitrogenated function that could be transformed into a primary amino group, such as nitro or azido. In several cases,^{16,23} the resulting isocyano-anilino complexes were transient undetected species that quickly converted into the final isolated reaction products, the respective diamino carbene complexes **14** (Scheme 6).

However, this is not a general behaviour, as in other cases, depending on the metal M and the additional ligands Ln , the intermediate amino-isocyano complexes **12** could be isolated and characterized, as shown in Fig. 1.^{23c,d,24}

Back to uncomplexed 2-isocyananilines, despite the considerations above, we found a few stable and characterized members of this class of compounds appearing in the chemical literature. Thus, we found some derivatives of the parent 2-isocyananiline monosubstituted at the amino group, retaining one N-H bond.²⁵ It seems reasonable to postulate that these compounds would also undergo the intramolecular insertion of the isocyanide function into the N-H bond for finally yielding 1-substituted benzimidazoles, in a similar way to what occurs in the parent compound. However, we presumed that the nature of the substituent on the amino N atom



Scheme 5 The equilibrium between 2-metalled-benzoxazole(-benzothiazole, -benzimidazole) and their open-chain isomers.



Scheme 6 Formation of carbene complexes **14**.

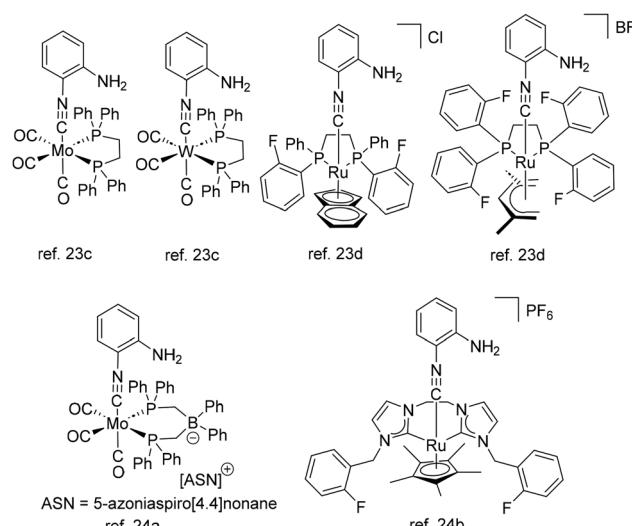


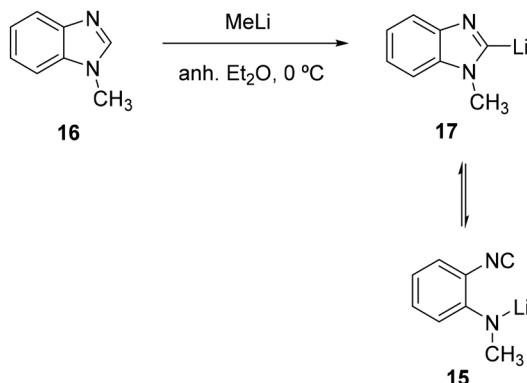
Fig. 1 Amino-isocyano complexes **12**.

could modulate the rate of such an insertion reaction, and so the reported examples of this class of 2-isocyananilines, not rapidly converting into the respective benzimidazoles, could give us hints for understanding the reasons behind their stability.

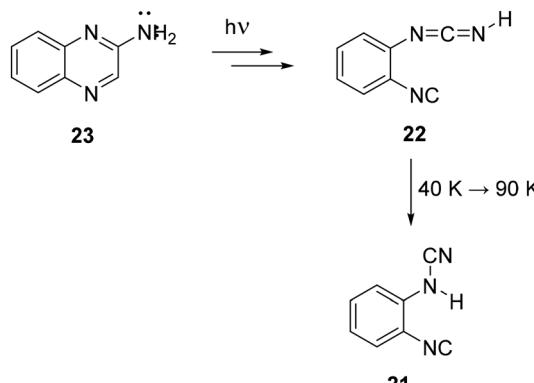
There is only one reported *N*-alkyl derivative of a 2-isocyananiline, the methyl derivative of the parent compound, although not as such species but in the form of its lithium salt **15**.^{22b} It was prepared by lithiation of 1-methylbenzimidazole (**16**) with MeLi at 0 °C in d^8 -THF and shown to be in equilibrium with the corresponding 2-lithio benzimidazole **17** (Scheme 7). This equilibrium is clearly apparent in the ^{13}C NMR spectrum of the mixture of open and cyclic isomers.

We located only one article showing a monosubstituted *N*-aryl derivative of a 2-isocyananiline, represented in Scheme 8 as **18**, $R = H$, $\text{Ar}^2 = 4$ -tolyl. The authors report on a visible-light-induced photoredox-catalyzed radical tandem cyclization of *o*-isocyano diarylamines **18** with arylthiodifluor-





Scheme 7 Formation of 2-lithio benzimidazole 17.



Scheme 9 Formation of (2-isocyanophenyl)phenyl cyanamide 21.

alkyl 2-pyridyl sulfones **19** (Scheme 8).²⁶ These reactions work with a broad range of substrates and provide a simple and efficient method for the synthesis of 11-difluoromethyl-substituted dibenzodiazepines **20** *via* the addition of the fluoroalkyl radical to the isocyano carbon atom and further cyclization of the resulting imidoyl radical.

In the experimental part of that paper, the starting *o*-isocyno diaryl amines are not adequately described as their full characterization and spectroscopic data are not reported. For this reason, we could not check the data supporting the structure of the compound claimed to be *o*-CN-C₆H₄-NH-C₆H₄-CH₃-*p*, the only diarylamine (with an NH fragment) among the starting materials in that work, mostly *N*-methyl partners. Furthermore, in some instances, the authors report a structure of *N*-substituted 2-isocyananiline despite the spectroscopic data not appearing to corroborate this.^{27,28}

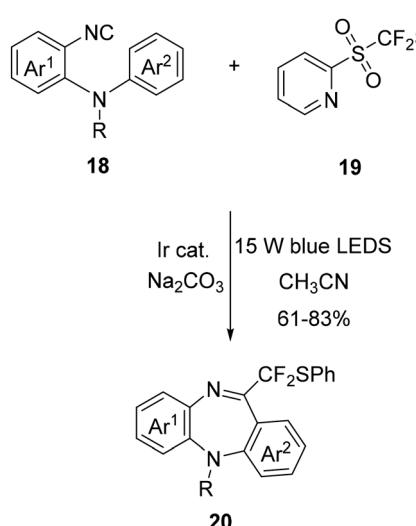
Some other 2-isocyananiline derivatives of our interest found in the chemical literature bear one electron-withdrawing substituent linked to the amino nitrogen atom. First, we will comment on (2-isocyanophenyl)phenyl cyanamide (21)

(Scheme 9). This species was spectroscopically characterized by C. Wentrup *et al.* in an Ar matrix at low temperature, but was not isolated. Compound **21** was formed by rearrangement of the precursor carbodiimide **22**, on warming from 40 K to 90 K in the Ar matrix.

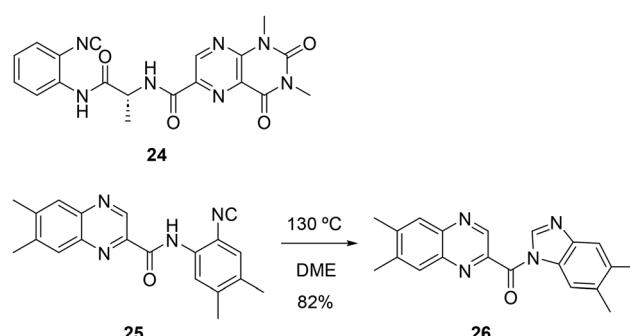
Carbodiimide **22** resulted from the photolysis of quinoxalino-nitrene **23**, which itself was formed by a flash-vacuum thermolytic treatment of tetrazolo[1,5-*a*]quinoxaline.²⁹

Very recently, a couple of 2-isocyananilides have been reported. The first one is a natural product containing an isocyanide group, the lumazine peptide **24** (Scheme 10) isolated from a Hawaiian fungal strain.³⁰ We located the second one in the supporting information of a recent paper dealing with an isocyanide heterodimerization-triggered three-component reaction, a publication by Dong, Xu and coworkers,³¹ in which the quinoxaline-2-carboxamide **25** derived from a 2-isocyananiline.

Unfortunately, the article did not disclose how this species was prepared, although we reasonably imagine that it could derive from the hydrolysis of an intermediate formed from an *o*-diisocyanobenzene homodimer. The important thing, however, is that it is stable enough for its isolation and manipulation, as the authors stated that it converted into the benzimidazole **26** under heating in DME solution at 130°C for 1 h, a cyclization process that follows the general trend of other 2-isocyananilines as shown above, although it required stronger thermal conditions.



Scheme 8 Formation of dibenzodiazepines 19.

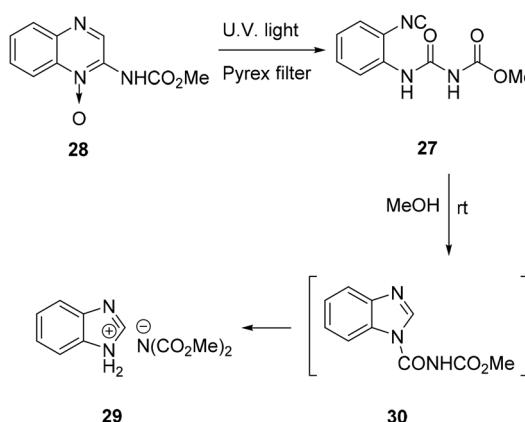
Scheme 10 Isocyanides **24** and **25** and formation of heterocycle **26**.

3. (2-Isocyanophenyl)carbamates

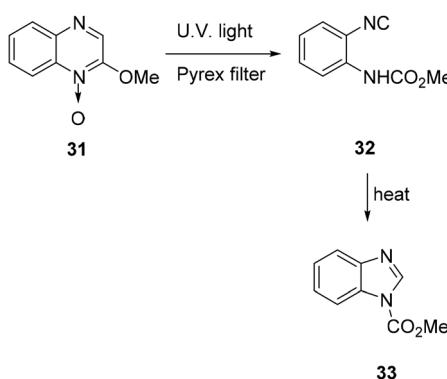
In old work by J. M. Cox *et al.*³² the 2-isocyanophenyl ureido-carboxylate **27** was reported as resulting from the irradiation of methyl quinoxalin-2-ylcarbamate 1-oxide (**28**) under acidic conditions (Scheme 11). The isocyanide **27** was isolated, crystallized from toluene and fully characterized. However, in methanol solution at room temperature, it slowly converted into benzimidazolium bis(methoxycarbonyl)amide (**29**), by following the habitual cyclization pattern to the corresponding benzimidazole **30** followed by methanolysis and dissociation.

Five years later, the Albini group investigated the photochemistry of related quinoxaline-1-oxides.³³ When the 2-methoxy derivative **31** was irradiated, the methyl (2-isocyanophenyl)carbamate **32** was obtained and characterized as a relatively stable compound (Scheme 12). In the words of the authors of this research, “... *this compound is thermally unstable and can only be crystallized (cyclohexane) in a quick operation. Otherwise, it reacts by insertion of the electron-deficient isocyano group into the amidic N–H bond to yield methyl benzimidazole-1-carboxylate **33**.*”

These latter examples apparently indicate that an EWG on the amino group contributes to stabilization of the isocyano anilines.



Scheme 11 Formation of benzimidazolium **29**.



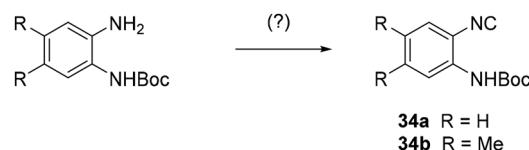
Scheme 12 Formation of benzimidazole **33**.

3.1. *tert*-Butyl (2-isocyanophenyl)carbamates

Last but not least, two additional examples of carbonyl-substituted 2-isocyananilines should be cited apart. In contrast to the thermally unstable and scarcely utilized methyl carbamate derivative **32** shown above, a couple of *tert*-butyl analogues, *tert*-butyl (2-isocyanophenyl)carbamates **34a,b** (Scheme 13), are apparently stable enough to be synthetically useful functionalized isocyanides. As a proof of that, both have been used in a number of multicomponent processes, characteristic of isocyanides, namely, the Ugi and Passerini reactions, as shown below.

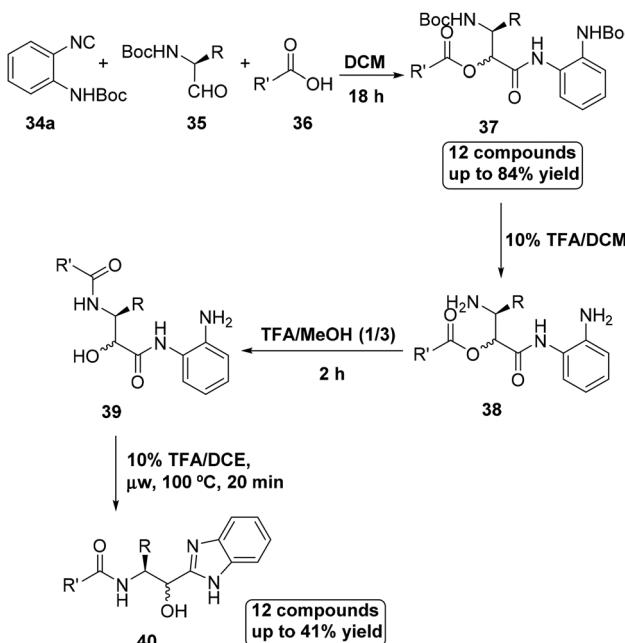
Remarkably, we were unable to find detailed experimental procedures describing the syntheses of compounds **34a,b**. The oldest reference where **34a** appears³⁴ did not show information concerning its preparation, whereas in the following paper on the time scale,³⁵ it was mentioned that these compounds were commercially available. In one of these articles,³⁶ a little piece of unprecise information on the preparation of **34a** was given, indicating that *N*-Boc-1,2-phenylenediamine was the starting material. Some additional details on **34a** appeared in one of the later publications on this isocyanide,³⁷ where it was stated that the reagent is formed *in situ* under acidic conditions. For completing this information, we consider appropriate to point out that the two most reasonable chemical precursors of **34a** are the above-mentioned *N*-Boc-*o*-phenylenediamine and *N*-Boc-*N'*-formyl-*o*-phenylenediamine.

In the usual multicomponent reactions underwent by isocyanides, *tert*-butyl (2-isocyanophenyl)carbamates **34a,b** proved to be ideal substrates to achieve more complex synthetic sequences than those obtained with simpler aryl isocyanides, taking advantage of the easy deprotection of their amino group at the end of the multicomponent process, thus enabling the occurrence of further intramolecular processes involving the free NH group. One of the early examples using *tert*-butyl (2-isocyanophenyl)carbamate **34a** to synthesize a heterocycle followed a Passerini reaction–amine deprotection–acyl migration reaction (PADAM) sequence.³⁵ This strategy involved a Passerini condensation between **34a**, carbamate-functionalized aldehyde **35** and carboxylic acid **36**, affording product **37** (Scheme 14). The subsequent double deprotection of the carbamate groups using a trifluoroacetic acid (TFA)/DCM mixture afforded diamine **38**. Interestingly, during this protocol, an acyl migration is accomplished, changing the position of the acyl group, which comes from the carboxylic acid reactant in the newly generated benzimidazole. This migration was carried out by stirring this product in trifluoroethanol (TFE)/MeOH, thus leading to **39**. The final microwave irradiation in a



Scheme 13 Formation of isocyanides **34**.

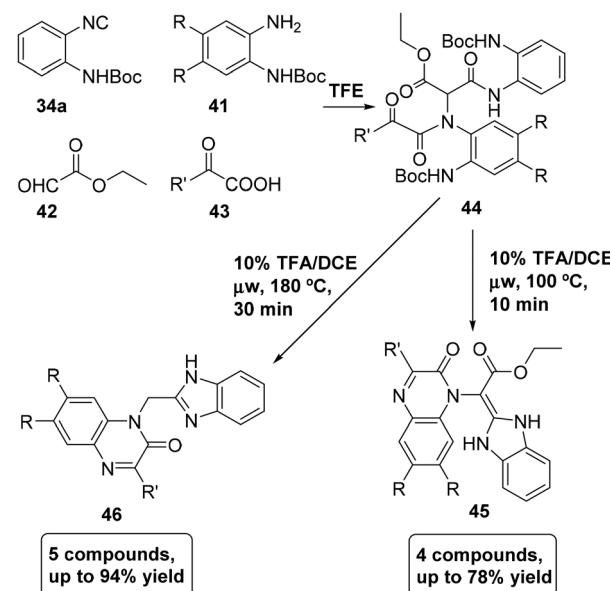




Scheme 14 Synthesis of benzimidazoles **40** using **34a** as the starting material.

TFA/1,2-dichloroethane (DCE) mixture afforded a series of benzimidazoles **40** through an intramolecular cyclization, constituting a convenient methodology for high-throughput synthesis.

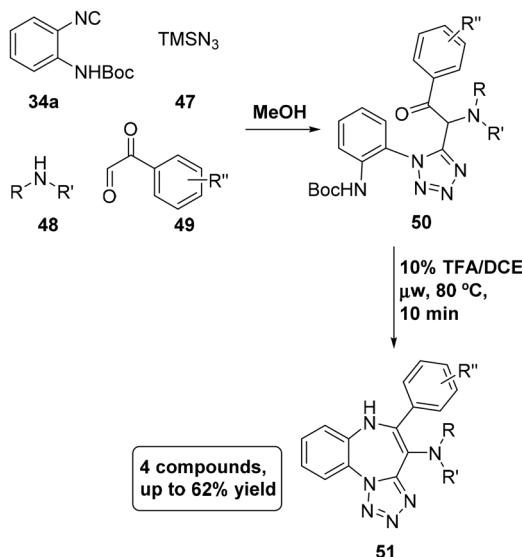
The Ugi reaction, which is a multicomponent reaction involving the employment of isocyanides, has been widely employed in the preparation of target heterocycles.^{6g,38} In this scenario, *tert*-butyl (2-isocyanophenyl)carbamates **34a,b** have made available a wide variety of heterocycles due to their interesting reactivity. One of the early examples employed **34a** to synthesize bis-heterocycles through a tandem Ugi-deprotection-cyclization-decarboxylation methodology.³⁹ The synthesis proceeded through the prior formation of a Schiff base between amine **41** and ethyl glyoxalate (**42**) using TFE as the solvent. Subsequently, isocyanide **34a** and carboxylic acid **43** were added, thus leading to the corresponding Ugi adduct **44** (Scheme 15). The heating treatment of adduct **44** under microwave irradiation using TFA in DCE resulted in the obtention of a series of benzimidazole-quinoxalines **45** through a tandem double ring formation. These cyclizations proceeded through the formation of a diamine-based intermediate *via* deprotection of the carbamate groups. Further treatment of some derivatives **45** using the same protocol but increasing time and temperature led to the decarboxylation of the products to form bis-heterocycles **46** in high yields. Interestingly, when using this protocol directly employing the suitable Ugi adducts **44**, the direct formation of the target benzimidazole-quinoxalines **46** was accomplished *via* a sequential deprotection-cyclodehydration-decarboxylation strategy. Remarkably, control over the bis-heterocycle that is formed is possible by changing the temperature and microwave irradiation time.



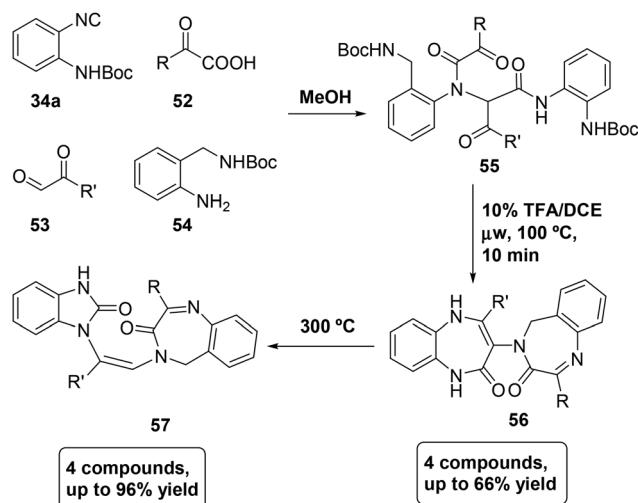
Scheme 15 Synthesis of benzimidazoles **45** and **46** through multicomponent Ugi reactions using **34a** as the starting material.

Besides the formation of benzimidazole rings, isocyanide **34a** has also been employed to obtain different target heterocycles, such as benzodiazepine-based scaffolds, which turn out to be highly valuable in the pharmaceutical industry.⁴⁰ This synthesis was accomplished through a four-component Ugi-azide reaction, which replaced the carboxylic acid with azidotrimethylsilane (**47**). In this protocol, the azide acts as a nucleophile, trapping the nitrilium intermediates, which undergo intramolecular cyclization in order to provide the corresponding tetrazole. Thus, the multicomponent reaction of **34a**, **47**, amine **48** and arylglyoxaldehyde **49** led to the formation of a series of adducts **50** (Scheme 16). The subsequent microwave treatment using a TFA/DCE mixture yielded benzodiazepines **51** in moderate yields through the sequential deprotection-cyclization of the Ugi adduct.

The stereoselective synthesis of benzimidazol-2-one derivatives employing compound **34a** as one of the components that yields the intermediate Ugi adduct has been reported through the formation of a benzodiazepine-based compound.⁴¹ The synthetic protocol was initiated through a Ugi reaction employing **34a**, carboxylic acid **52**, glyoxaldehyde **53** and amine **54**, which yielded adduct **55** (Scheme 17). The subsequent microwave irradiation in TFA/DCE afforded the bis-heterocyclic 1,5-benzodiazepine-1,4-benzodiazepine **56** in moderate to good yields. The subsequent heating of this compound promoted a rearrangement that afforded the target benzimidazol-2-ones **57**, showing only the *Z* configuration, in excellent yields. This protocol allows different heterocycles of interest to be obtained depending on the cascade of events taking place, thereby illustrating once again the versatility of isocyanide **34a** in the synthesis of a wide variety of relevant molecules. Indeed, while stopping the reaction after microwave irradiation leads to bis-



Scheme 16 Synthesis of dibenzodiazepines **51** using **34a** as the starting material.



Scheme 17 Synthesis of bis-benzodiazepines **56** and *Z*-benzimidazole-2-ones **57** using **34a** as the starting material.

benzodiazepines, further thermal treatment stereoselectively yields different bis-heterocyclic compounds.

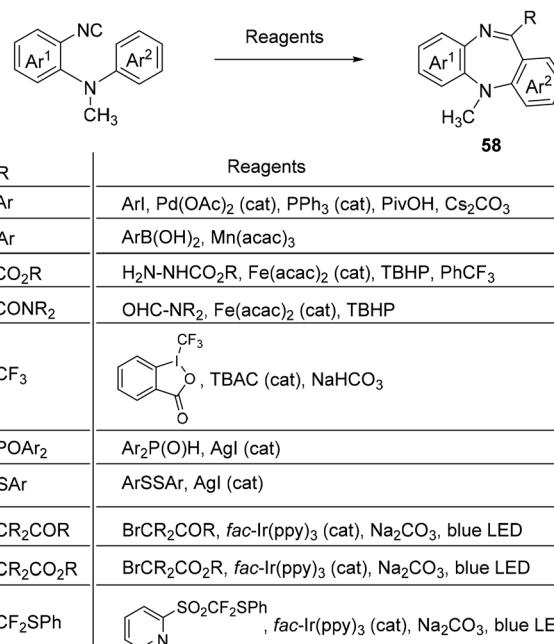
The combination of a Ugi reaction followed by a tandem deprotection reaction-intramolecular cyclization protocol, using *tert*-butyl (2-isocyanophenyl)carbamates **26a,b** as starting materials, has facilitated the preparation of a vast pool of heterocycles, such as benzodiazepines,⁴² bis-benzimidazoles,⁴³ hydantoins,⁴⁴ and pyrrolopyridinones.³⁷ However, undoubtedly, these isocyanides have found their privileged implementation in the preparation of benzimidazole-based derivatives in which this heterocyclic nucleus is fused to others, including piperazine,⁴⁵ isoquinoline,⁴⁶ diazepinone,⁴⁷ pyrazine,⁴⁸ quinoxalinone,⁴⁹ quinoxaline⁵⁰ and isoindolinone.⁵¹

4. *N,N*-Disubstituted 2-isocyanoanilines

Finally, at this point, the reader might wonder if *N,N*-disubstituted 2-isocyanoanilines are known and stable substances. A substructure SciFinder search for such species, counting those with two C-linked groups at the amino N atom, retrieved **56** of these compounds, discounting a few more in which the amino N atom is embedded into a heterocyclic nucleus. The vast majority of those **56** compounds were *N*-aryl-*N*-methyl derivatives (**50**) that have been used for radical or palladium-mediated additions at the isocyano carbon atom and further cyclizations (cycloimidoylations) on the nearby *N*-aryl group, yielding 5-methyl-11-substituted dibenzodiazepines **58** (Scheme 18).^{26,52}

Notwithstanding, the *N,N*-dimethyl, diethyl, dipropyl, diallyl or dibenzyl partners and similar species combining two of these simple alkyl groups at the amino N atom, among the examples of *N,N*-disubstituted 2-isocyanoanilines, have not been reported up to now.

This is the reason behind our belief that the more nucleophilic the amino group of the 2-isocyanoanilines is, the more unstable these compounds are. Such assumption is in concordance with the proved stability of the mono-Boc derivatives commented above, bearing a N atom of diminished nucleophilicity, and also with the apparent stability of a wide range of related phenylisocyanides with an *ortho* N atom lacking nucleophilic characteristics because it is embedded into an heteroaromatic ring (pyrrole, indole, imidazole, benzimidazole, 1,2,3- and 1,2,4-triazole, tetrazole, and others).⁵³



Scheme 18 Synthesis of dibenzodiazepines **58**.



5. Conclusions

From browsing the reported examples of 2-isocyanoanilines, with attention to the preparation, stability and chemistry of the scarce *N*-monosubstituted derivatives, some conclusions can be drawn: (i) the parent, 2-isocyanoaniline, is an unstable non-isolated compound, quickly converting into its cyclic isomer, benzimidazole, under normal conditions; (ii) *N*-alkyl or aryl monosubstituted derivatives (still with one N–H bond) are practically unknown; (iii) a carbonyl group linked to the amino N atom (derivatives with an NH–CO fragment) apparently confers stability to these species, when compared with the parent compound and alkyl/aryl monosubstituted analogues; (iv) by heating in solution, some of these NH–CO derivatives are converted into the respective 1-acyl benzimidazoles; and (v) the NH–Boc fragment is particularly efficient in stabilizing the 2-isocyanophenyl NH species, apparently allowing the isolation and characterization of the two reported examples as well as their synthetic applications.

To our knowledge, the instability of 2-isocyanoanilines and some of their NH-substituted derivatives has been neither generally recognized up to now, and for this reason, nor rationalized. The observed conversion of these compounds into their cyclic isomeric benzimidazoles can be understood as resulting from the isocyanide insertion into the *ortho*-positioned N–H bond. This type of reaction, the insertion of NC groups into N–H bonds, is a known process although it generally requires the catalysis of Lewis acids or transition metals.^{4a} However, NH 2-isocyanoanilines seem to cyclize in the absence of such catalysts, and the insertion reaction most probably occurs due to the proximity between the two reactive functionalities. With the data presented above, the postulation of a precise general mechanism of these cyclizations is still a challenge. We are currently involved in its study by computational means, exploring diverse potential mechanistic routes, both unimolecular and bimolecular, concerted and stepwise. In close connection with this, we are also investigating the reasons behind the stability of the mono-Boc derivatives shown above. Hopefully, the results of such computational studies will be disclosed elsewhere in the near future.

In view of the privileged reactivity of these compounds, the synthesis of numerous novel heterocycles through multicomponent reactions starting from 2-isocyanoanilines is expected, particularly those showing therapeutic activity. In addition, it is envisioned that the direction of research in this area will be focused on the development of new methods of stabilization of 2-isocyanoanilines, thus increasing the scope of the target compounds which can be synthesized.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

Acknowledgements

This work was supported by the MICINN (PID2020-113686GB-I00/MCIN/AEI/10.13039/501100011033) and Fundacion Seneca-CARM (Project 21907/PI/22). A. S.-S. gratefully acknowledges “la Caixa” Foundation (ID 100010434) for a fellowship (LCF/BQ/PR24/12050020).

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