Anodic Oxidation of Aminotetrazoles: A Mild and Safe Route to Isocyanides

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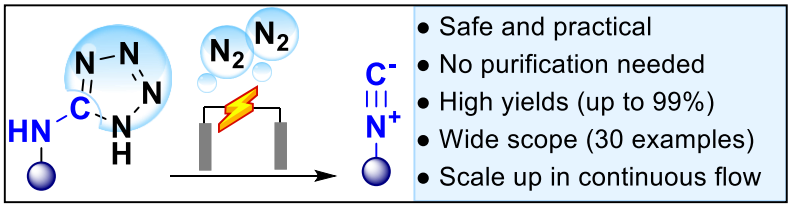
Electronic Supplementary Information Supporting Information Placeholder



ABSTRACT: A new electrochemical method for the preparation of isocyanides from easily accessible aminotetrazole derivatives has been developed, which tolerates an unprecedented range of functional groups. The use of chemical, rather than electrochemical, oxidation to afford isocyanides was also demonstrated, which provides access to these compounds for those without electrosynthesis equipment. The practicality of scale-up using flow electrochemistry has been demonstrated, in addition to the possibility of using electrochemically generated isocyanides in further reactions.

INTRODUCTION

In recent years, innovative approaches for the synthesis of high value chemicals have been developed, with the aim of reducing the ecological footprint of chemical synthesis. Electrosynthesis has played a significant role in achieving this aim, as it reduces the need for stoichiometric redox reagents, harsh reaction conditions, and can be easily scaled-up.[1] Some recent examples of organic electrosynthesis include the mild and practical synthesis of orthoesters,[2] allylic oxidation of alkenes,[3] cross-coupling of phenols,[4] cyclobutanol ring expansions,[5] and intramolecular hydroamidation.[6]

Isocyanides are versatile building blocks in which the carbon center can act as both a nucleophile and electrophile.[7] They have been shown to exhibit significant antibiotic, antifungal, and antineoplastic activity.[8,9] Consequently, they are of significant interest to the synthetic community, due to the wide range of reactions that they can take part in, including Ugi-[10] and Passerini-type[11] multicomponent reactions (MCRs), insertions into carbon-metal σ-bonds,[12] and *N*-heterocycle formation.[13–17] Moreover, isocyanides have shown several noteworthy applications, such as ligation reactions with glycans for metabolic labelling studies and the preparation of carbazole-based polymers.[18,19] However, despite their early discovery and wide applications, conventional methods to access them have proven to be impractical[7] and significant safety concerns arise from their preparation.

Initially, isocyanides were synthesized via the substitution of alkyl halides in the presence of silver cyanide which, aside from being highly toxic, is far from being cost-effective when conducted at large scale (Figure 1).[20] The most common method for isocyanide synthesis is through the dehydration of unstable formamides in the presence of phosgene.[9] Nevertheless, this remains a high risk, hazardous, and expensive method at both small- and large-scales, and is incompatible with most common functional groups, especially amides.

Attempts have been made in recent years to address these concerns, with current alternatives featuring the use of cyanuric chloride,[21] $POCl_3$,[22] and PPh_3/CCl_4.[23] More recently, Gassman reported a one-pot protocol for converting alcohols into isocyanides using trimethylsilyl cyanide;[24] however, this method and its later iterations are time-consuming and are limited to benzylic and tertiary alcohols.[25–28]

To the best of our knowledge, only one synthetically relevant electrosynthesis has been reported for the preparation of isocyanides via a controlled potential electro-reduction of toxic and unstable carbonimidoyl dichlorides using a mercury cathode and an unpractical divided cell.[29] Herein, we report the development of a new, practical, support electrolyte-free and purification-free method for the synthesis of highly desirable isocyanides from ubiquitous carbonyl compounds via their readily accessible, crystalline and bench stable aminotetrazole derivatives.

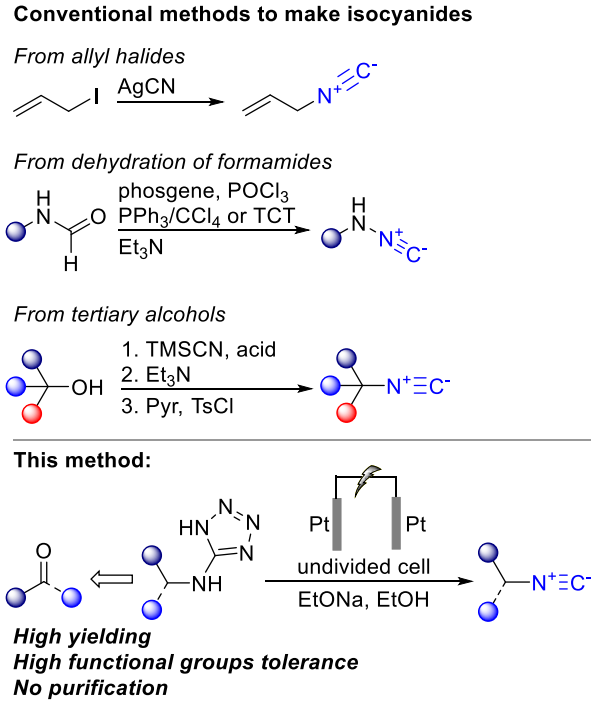
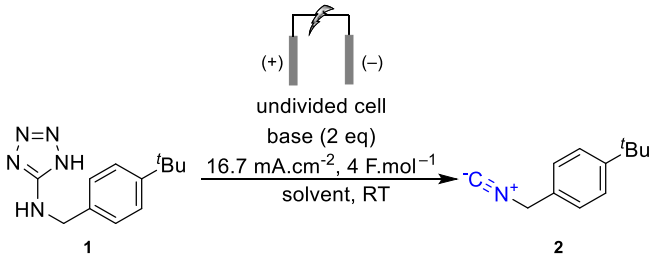


Figure 1. Summary of current methods for the synthesis of isocyanides

RESULTS AND DISCUSSION

In a seminal report, Höfle and Lange reported that aminotetrazoles could form isocyanides when treated with an unstable and toxic hypobromite solution.[30,31] Much to our surprise, only three unfunctionalised alkane examples have ever been reported, owing to the use of bromine and highly basic conditions, which renders the method incompatible with most functional groups. They also deemed anodic oxidation to be an unpromising alternative. Nevertheless, this provided a starting point for our electrochemical studies. In one step, tetrazole **1** was readily synthesized through reductive amination of the corresponding aldehyde with the inexpensive and commercially available 5-aminotetrazole (see Supporting Information). The anodic behaviour of **1** was studied by cyclic voltammetry (see Supporting Information). Tetrazole **1** displays a single chemically non-reversible oxidative event at ca. 1.1 V vs Fc. Electrode polishing was necessary between scans, owing to significant electrode fouling, which precluded further studies. However, upon adding one equivalent of collidine, a shift to lower potential (ca. 0.8 V vs Fc) was observed, presumably due to the formation of **1**'s anion. Additional equivalents of base led to complete suppression of any electrode fouling and further shift of the oxidative process to lower potentials.

Table 1. Optimization studies for the anodic oxidation of aminotetrazoles



Entry[a]	A/C	Current/mA	Base	Solvent	Yield/%[b]
1	C_{gr}/C_{gr}	50	NaOMe	MeOH	84
2	Pt/C_{gr}	50	NaOMe	MeOH	63
3	Pt/Pt	50	NaOMe	MeOH	99
4	Pt/Pt	25	NaOMe	MeOH	94
5	Pt/Pt	100	NaOMe	MeOH	81
6	Pt/Pt	50	LiOH	MeOH	57
7	Pt/Pt	50	NaOH	MeOH	56
8	Pt/Pt	50	Et_3N	ACN	28
9	Pt/Pt	50	NaOMe	MeOH/H_2O[c]	0
10	Pt/Pt	50	Et_3N	ACN/H_2O[d]	27
11[e]	**Pt/Pt**	**25**	**NaOEt**	**EtOH**	**98**

[a] Reaction conditions: **1** (0.3 mmol), base (0.6 mmol), solvent (5 mL), Pt foil working and counter electrode, 4 $F.mol^{-1}$, RT. [b] Yields determined by GC-MS analysis using dodecane as internal standard. [c] 1:1 mixture. [d] 9:1 mixture. [e] Due to the highly resistant nature of the solvent, the applied current was set to 25 mA

When **1** was electrolyzed with an applied current of 50 mA using carbon graphite electrodes in a basic methanolic solution, the corresponding isocyanide, **2**, was cleanly formed in 84% yield upon workup, without any noticeable heat increase of the solution (Table 1, entry 1). Optimization studies for this reaction (Table 1) revealed that the highest yields could be obtained using platinum foil working and counter electrodes and a current density of 16.7 $mA.cm^{-2}$ after 4 $F.mol^{-1}$ of charge had been passed through a 0.06 M methanolic solution of tetrazole **1** (Table 1, entry 3). Interestingly, replacing methanol with a greener solvent such as ethanol proved to give comparable yields, even if a lower current density had to be used due to the higher impedance of the solvent (Table 1, entry 11). Furthermore, electrolyses performed in ethanol were shown to have a higher functional group tolerance (e.g. esters) and a significantly reduced number of side products formed.

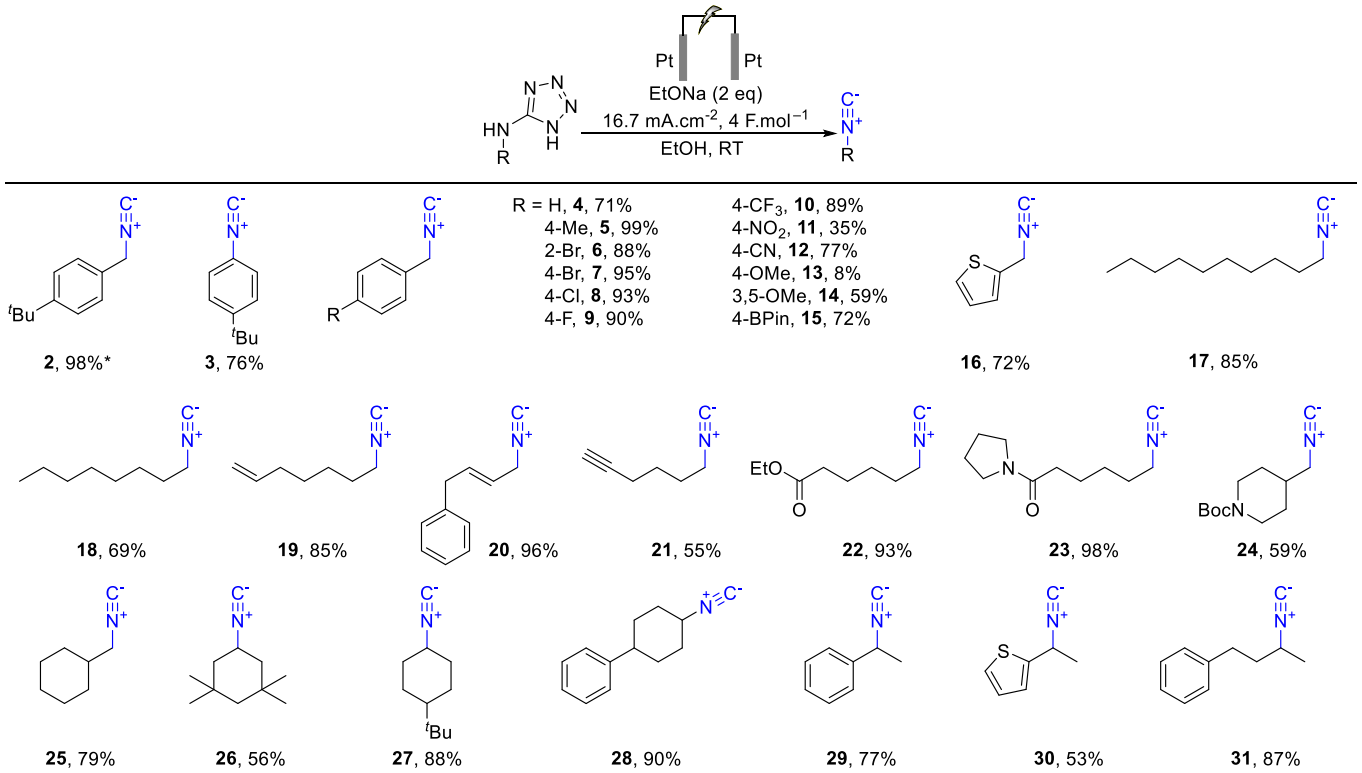
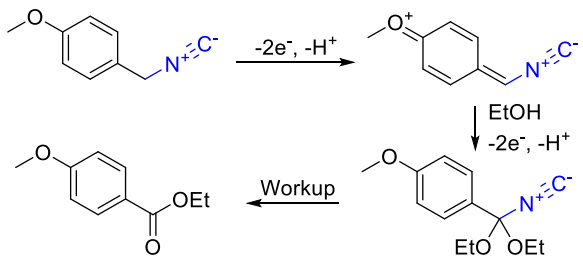


Figure 2. Substrate scope for the electrochemical synthesis of isocyanides from aminotetrazole derivatives. *A similar yield was obtained on both 0.3 mmol and 1 mmol scale.

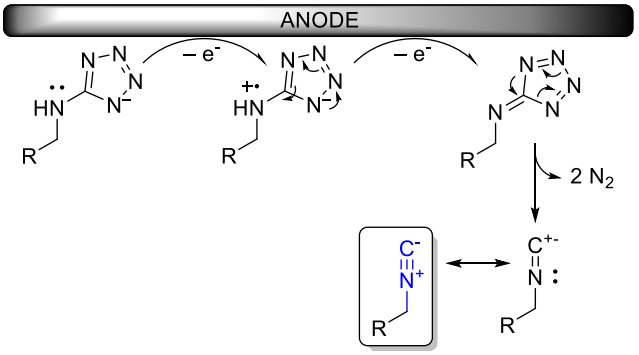
With the best conditions in hand, a range of substituted tetrazoles were subjected to batch electrolysis to determine the scope and limitations of this new methodology (Figure 2). Excellent yields were obtained for alkyl-substituted aromatic and benzylic tetrazoles (**2–5,** > 71–98%), and no detrimental effects were observed upon the incorporation of halides or other electron-withdrawing groups (**6–10**, 88–95%). Although a lower yield was observed for **11**, this result is still noteworthy since usually nitro groups are electroactive under usual electrosynthetic conditions and lead solely to degradation. However, some challenges were encountered when electron-donating groups were introduced (**13**, **14**), most notably when a methoxy group was introduced in the *para*-position (**13**, 8%), with the main product being the ethyl ester instead. This is likely due to overoxidation of the product, which leads to the formation of a highly reactive quinoid methide (Scheme 1). The addition of ethanol onto the quinoid methide and further oxidation eventually results in the formation of the ethyl ester. Our method is also tolerant of borane derivatives (**15**, 72%) thus providing the opportunity for further chemistry at a later stage by means of Pd-catalyzed cross-coupling chemistry.

The synthesis of alkyl-substituted isocyanides was similarly well-tolerated, including those that featured unsaturated C=C and C≡C bonds (**17–19**, 76–92%). Remarkably, even esters and amides, which are not tolerated by classical chemical dehydration methods, gave respectable yields using our electrochemical conditions (**22–24**, 59–93%). Our method also afforded isocyanides where the aminotetrazole precursor was derived from ketones rather than aldehydes, with alkyl, aryl, and heteroaromatic systems giving good to excellent yields (**26**–**31**, 53–90%).

Scheme 1. Proposed overoxidation of isocyanide 13, resulting in the formation of a quinonoid methide intermediate



Scheme 2. Proposed mechanism for the formation of isocyanides from aminotetrazoles



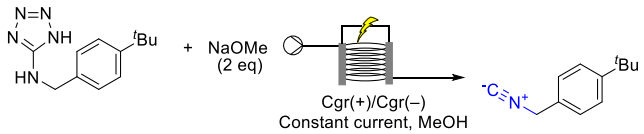
A possible mechanism for the electrochemical synthesis of isocyanides from aminotetrazole derivatives is outlined in Scheme 2. First, the tetrazole is deprotonated through the addition of base. The anion is then anodically oxidised to form an unstable fulvene, which rapidly loses two molecules of nitrogen and forms the desired isocyanide.

In order to demonstrate the practicality of our method and its potential use at a larger scale, we chose to translate it into a continuous flow setup (Scheme 3). The use of continuous flow chemistry to produce large quantities of value-added chemicals is well known, and scale-up can be achieved with relative ease.

Optimization studies were conducted using 0.1 mmol of tetrazole **1** in methanol rather than ethanol, as the former was found to be much more solubilising and therefore less prone to the fomation of blockages in the flow setup. Carbon graphite electrodes were chosen over platinum, as they are more economically viable when moving to large-scale synthesis.

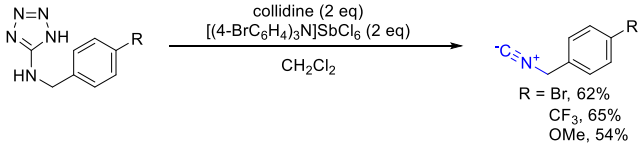
The applied current and residence time in the electrochemical cell (cell volume: 225 µL) were varied (see Supporting Information), with the highest yield (81%) obtained using an applied current of 400 mA and a flow rate of 225 µL.min^{-1}, achieving an improved Faradic yield of 80% (2.5 F.mol^{-1}). With the best conditions in hand, we sought to electrolyze 1 g of tetrazole **1** by attachment of a reservoir of tetrazole (0.1 M) in basic methanol. To our delight, it was possible to isolate the desired isocyanide in excellent yield (93%) after workup, thus demonstrating the practicality of scale-up for our new method.

Scheme 3. Flow electrochemical synthesis of isocyanide 2



As a proof of concept, we also endeavoured to develop a chemical method for the synthesis of isocyanides, which possesses the benefit of being more accessible to the chemical community at large, given that electrosynthesis equipment is not yet commonplace in most synthetic laboratories. Magic Blue, *tris*(4-bromophenyl)ammoniumyl hexachloroantimonate, was an ideal candidate to achieve this task, as its oxidation potential is higher than that of deprotonated tetrazole **1** (Magic Blue $E_{½}$ = 0.65 V vs Fc), and it is a well-established, mild, and commercially available one-electron chemical oxidant. It was possible to perform the oxidation in dichloromethane, a solvent which is usually not conductive enough to be used without additional supporting electrolyte in electrosynthesis.

Scheme 4. Chemical oxidation of aminotetrazole derivatives using Magic Blue

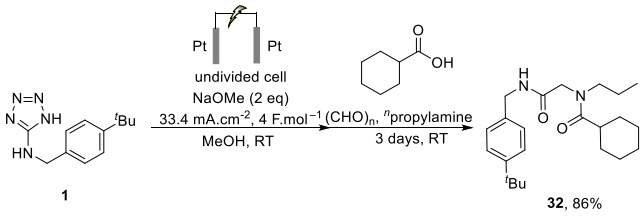


It was found that addition of two equivalents of collidine to a suspension of tetrazole in CH_2Cl_2 followed by two equivalents of Magic Blue afforded the desired isocyanide after only 10 minutes (Scheme 4). Purification by flash chromatography afforded isocyanides **7** and **10** in good yields (62 and 65% respectively) in addition to spectroscopically pure *tris*(4-bromophenyl)amine, which could be easily and rapidly recycled back into Magic Blue by reaction with $SbCl_5$ in CH_2Cl_2, to be reused in later reactions.

Much to our delight, this chemical method does not result in the overoxidation of isocyanide **13**, as observed when using electrochemical methods, and a good yield was obtained after purification by flash chromatography (54%), with none of the corresponding ethyl ester observed by GCMS or NMR analyses.

With the development of both chemical and electrochemical methodologies, we attempted to engage our synthesized isocyanides in further reactivity. It was found that, after electrolysis of tetrazole **1** using our standard conditions, it was possible to achieve a one-pot Ugi condensation with cyclohexane carboxylic acid, paraformaldehyde, and propylamine (Scheme 5). Appealingly, no change of solvent was required, nor were any purifications of the intermediary isocyanide or final product, with an excellent yield of 86% obtained over two steps.

Scheme 5. Electrochemical synthesis of isocyanide 2, followed by immediate Ugi condensation reaction



CONCLUSIONS

In conclusion, a new electrochemical method to access isocyanides has been disclosed, which centers on a new disconnection approach whereby carbonyls can be considered as isocyanide precursors. This method has provided access to the desired products in excellent yields without the use of toxic reagents, harsh conditions, or wasteful supporting electrolyte. Moreover, unprecedented functional group compatibility was observed, with a broad substrate scope finally achieved for this class of compounds, with many isocyanides synthesized for the first time. Further applications of the isocyanides have also been evaluated, such as their involvement in Ugi-type multicomponent reactions. An alternative route to isocyanides using "Magic

Blue" as a chemical oxidant has also been demonstrated. Lastly, the method was shown to be easily scalable by means of flow electrochemistry, further proving its applicability in both academic- and industrial-scale laboratories.

ASSOCIATED CONTENT

(The Supporting Information is available free of charge at XXXX. Synthetic procedures, spectral data, compound characterization.

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