Electrochemical isothiocyanation of primary amines

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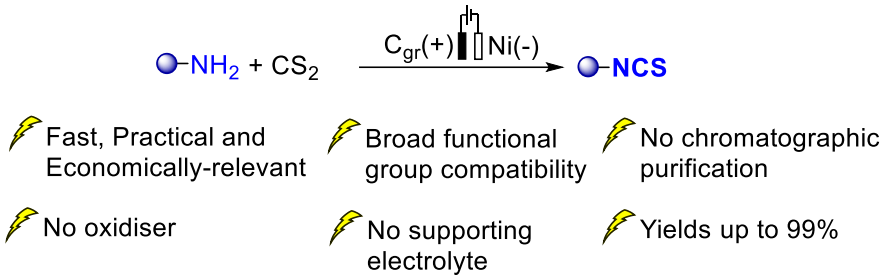
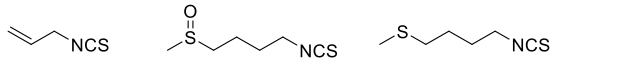
Supporting Information Placeholder



ABSTRACT: Isothiocyanates are ubiquitous building blocks used across the fields. Nevertheless, their classical syntheses very often rely on the use of toxic and expensive reagents. Herein we report a new practical, mild, high-yielding and supporting-electrolyte free electrochemical method for the preparation of aliphatic and aromatic isothiocyanates from amine and carbon disulfide.

Isothiocyanates are commonly encountered across the fields. For instance, in natural products, such as cruciferous vegetables and mustard oils, they are synthesised from the enzymatic conversion of glucosinolates.[1] Allyl isothiocyanate present in horseradish and wasabi, gives them their acrid taste.[2] Isothiocyanates also exhibit desirable biological activities. Sulforaphane and 4-(methylthio)butyl isothiocyanate have noticeable anticancer properties (Figure 1).[3] In medicinal chemistry, isothiocyanates represent valuable building blocks for the construction of *S*-heterocycles and thioureas which display antihypertension, anticancer, antidiabetic, anti-inflammatory, and antiviral properties.[4,5] Similarly, in agrochemistry, such thioderivatives are used as herbicides and anti-fungal agents.[6] Over the past 40 years, research regarding isothiocyanates has intensified considerably and several procedures for converting amines into isothiocyanates have been developed. However, most of them rely on reacting a primary amine with highly toxic, wasteful, or expensive thiocarbonyl transfer agents (Figure 2).[4,7] These methods are also very often limited in scope and in some cases, form a significant amount of undesired thiourea.[8]



allyl isothiocyanate Sulforaphane 4-(methylthio)butyl isothiocyanate

Figure 1. Structure of naturally occurring isothiocyanates

Other methods rely on the condensation of a primary amine with carbon disulfide followed by the use of oxidisers or desulfurisation agents. An elegant approach has been showcased by Munch *et al.* using di-*tert*-butyl dicarbonate (Boc_2O) as an efficient desulfurisation agent.[9] The reaction leads to the desired isothiocyanate and only produces volatile by-products. However, this protocol requires the use of a significant excess of carbon disulfide and suffers from limited functional group compatibility in addition to the non-negligible cost of Boc_2O. Acetyl and tosyl chlorides have also been reported as cheaper alternatives to Boc_2O to perform the desulfurisation step, yet leading to by-products that very often require chromatographic separations.[10] Another desulfurisation method developed by Xu *et al.* relies on using persulfate.[11] The methodology displays an excellent functional group tolerance, yet requires the isolation of the hygroscopic dithiocarbamate salt in order to obtain the desired isothiocyanates in good yield.[12] Although a one-pot alternative has been reported, the procedure is still lengthy and generates a significant amount of salts as by-products, thus leaving space to develop a more efficient and faster route to isothiocyanates.

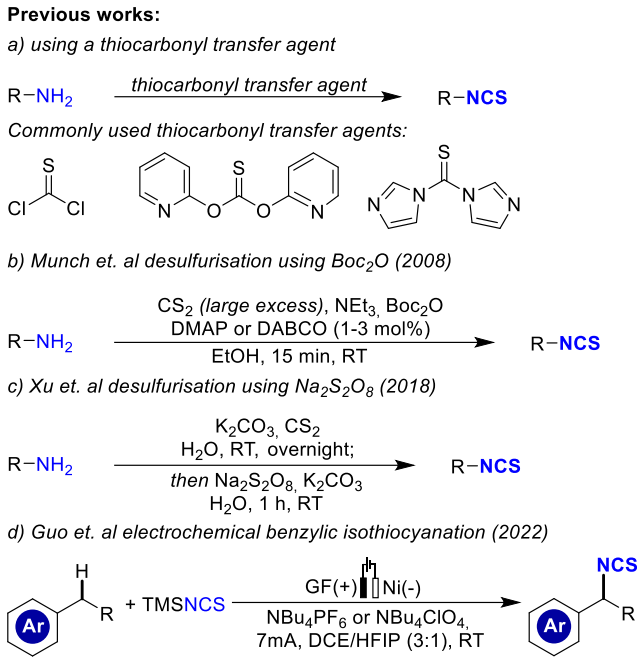


Figure 2. Approaches to the synthesis of isothiocyanates

Electrochemistry opens the door to new chemical transformations by using electricity as one of the cheapest reagents.[13–15] Zhang and co-workers have recently disclosed an electrochemical isothiocyanation of alkylbenzene derivatives, yet the transformation is restricted to benzylic positions and uses a significant amount of wasteful supporting electrolyte.[16] Herein we describe a new general, practical and supporting electrolyte-free electrochemical conversion of primary amines into isothiocyanates (Figure 3).

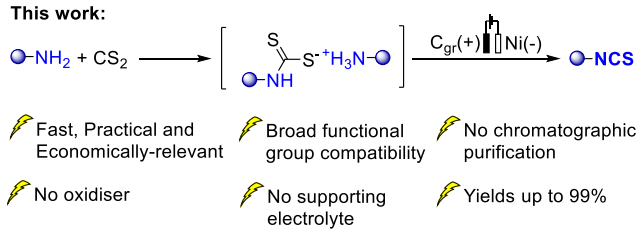
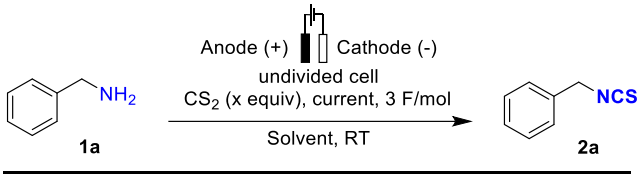


Figure 3. Proposed approach to the synthesis of isothiocyanates

Our overall approach consists of condensing a primary amine with carbon disulfide (CS_2) to form a dithiocarbamate salt *in-situ*, followed by its anodic desulfurisation. We started our investigation by optimising the isothiocyanation of benzylamine (**1a**) as a model substrate. As expected, the amine condensation with carbon disulfide proved to be a crucial step in the overall transformation. Indeed, adding CS_2 to an 80 mM solution of the amine followed by electrolysis only afforded the desired isothiocyanate in 20% yield (Table 1, Entry 3), presumably due to an incomplete condensation reaction. Much to our delight, when 5 equivalents of CS_2 were added neat to the amine, followed by the solvent, the electrolysis of the solution provided **2a** in 95% yield (Entry 14). As an anode material, carbon graphite (C_{gr}) led to slightly higher yields than platinum (entries 6 and 7). As the cathode, nickel proved to be the optimal material, presumably due to its low hydrogen overpotential, thus favouring the reduction of the protons and avoiding any undesired cathodic side reactions.[17] Finally, methanol and a low current of 5mA (J= 1.67 mA.cm^{-2}) afforded excellent chemical (95%) and faradic (91%) yields for the desired isothiocyanate. In most cases, the final compounds were obtained pure after a simple acidic workup.

Table 1. Summary of optimisation for the primary alkyl amine transformation



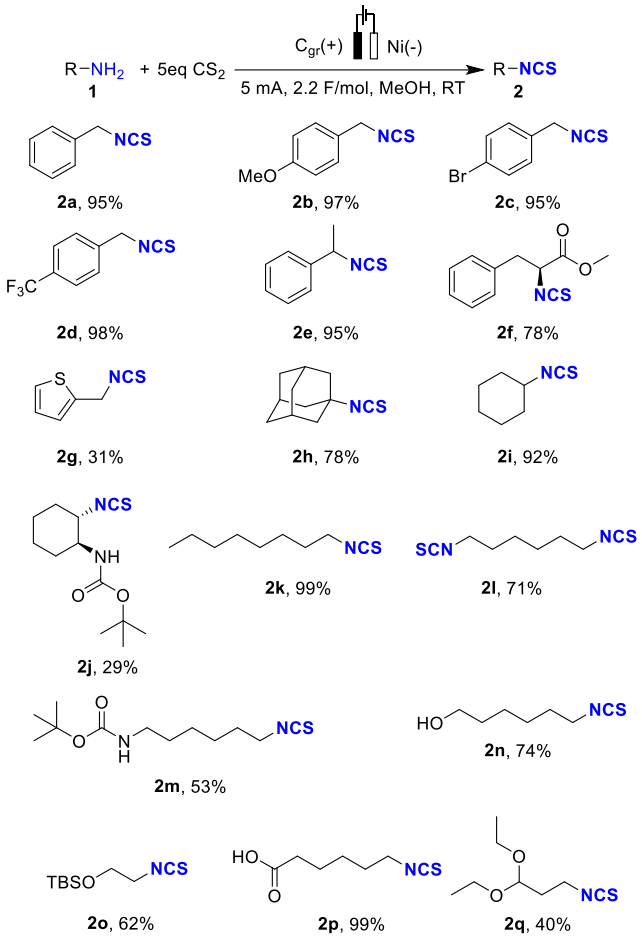
Entry	Anode	Cathode	CS_2	Solvent	Current (mA)	Yield[a]
1[b]	C_{gr}	C_{gr}	1.5	MeOH	20	14
2[b]	C_{gr}	C_{gr}	2.5	MeOH	20	22
3[b]	C_{gr}	C_{gr}	2.5	MeOH	20	20
4[b]	C_{gr}	C_{gr}	5	MeOH	20	20
5[b]	C_{gr}	C_{gr}	10	MeOH	20	22
6	Pt	Pt	2.5	MeOH	20	78
7	C_{gr}	C_{gr}	2.5	MeOH	20	85
8	C_{gr}	C_{gr}	2.5	EtOH	20	41
9	C_{gr}	Ni	2.5	MeCN	20	80
10	C_{gr}	Ni	2.5	MeOH	50	12
11	C_{gr}	Ni	2.5	MeOH	10	82
12	C_{gr}	Ni	2.5	MeOH	5	84
13	C_{gr}	Ni	5	MeOH	5	90
14[c]	**C_{gr}**	**Ni**	**5**	**MeOH**	**5**	**95**
15[c]	C_{gr}	C_{gr}	5	MeOH	5	67

[a] All yields displayed are isolated yields for **2a**. [b] Experiment done by adding CS_2 to an 80 mM solution of the amine. [c] Experiment done with 2.2 F/mol.

With the best conditions in hand, the scope and limitations of the methodology were explored by electrolysing a series of amines bearing different functional groups (Scheme 1). On benzylic amines, both electron-donating (*para*-methoxy benzylamine, **1b**) and electron-withdrawing groups (*para*-trifluoromethyl benzylamine, **1d**) were compatible with our electrolysis conditions and afforded **2b** and **2d** in nearly quantitative yields. Interestingly, in the cases of benzylic amines bearing an electron-withdrawing group, such as **1c** and **1d**, 10 equivalents of CS_2 were necessary to afford **2c** and **2d** with good yields. Using a lower amount of CS_2 mainly led to the formation of the symmetrical thiourea. Racemic 1-phenylethylamine **1e** was successfully converted into the isothiocyanate **2e** and an isothiocyanate derivative of L-phenylalanine methyl ester (**2f**) has been obtained in good yield. Our method also tolerates easily oxidisable groups such as thiophene **2g**. Thereafter, our investigations led us to test out saturated cyclic compounds (**2h, 2i, 2j**), which gave moderate to excellent yields. Aliphatic primary amines were also tested (**2k – 2q**), and all gave satisfactory yields for the desired isothiocyanates. Diamine **1l** gave the anticipated diisothiocyanate **2l** in good yield. As expected, an applied current of 5mA for 4.4 F/mol and 10 equivalents of CS_2 were necessary to carry out this diamine conversion. In addition, the mono Boc-protected diamine **1m** was equally well tolerated

with our method. A free, unprotected hydroxyl group was tested and afforded **2n** in satisfactory yield. Silyl ether **1o** has also been successfully converted to isothiocyanate **2o**. Finally, carboxylic acids and acetals showed to be compatible with our method and provided **2p** and **2q,** respectively, in excellent and moderate yields.

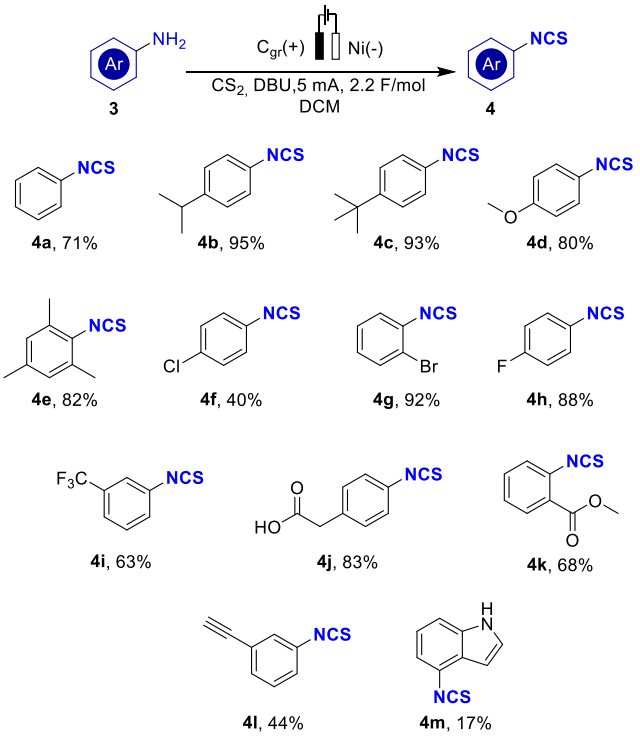
Scheme 1. Substrate scope for the electrochemical conversion of primary alkyl amines to isothiocyanates



All yields indicate pure and isolated product

Encouraged by the excellent results obtained on aliphatic amines, an attempt was made at using the previously optimised conditions for the isothiocyanation of aniline derivatives, unfortunately, without great success. As expected, the lower nucleophilicity of aniline derivatives precluded their efficient addition onto CS_2.[18] In this case, an external base was required to form the desired dithiocarbamate salt. Screening of the experimental conditions to transform aniline into isothiocyanatobenzene (table S2) led to replacing methanol with dichloromethane and adding 5 equivalents of DBU. Besides acting as a base, DBU is also known to catalyse the addition of nucleophiles on CS_2.[19] With these conditions in hand, the scope and limitations of the novel electrotransformation were investigated on aromatic substrates (Scheme 2).

Scheme 2. Substrate scope for the electrochemical conversion of primary aryl amines to isothiocyanates.



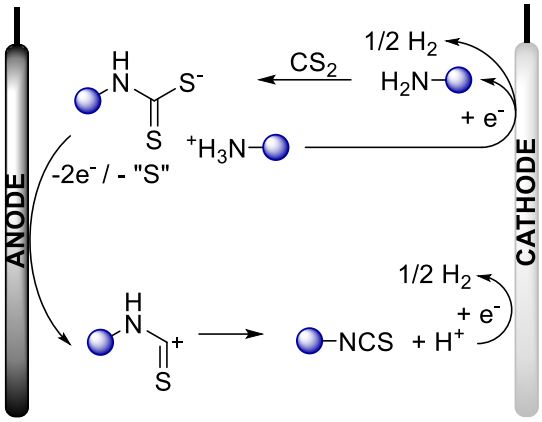
All yields indicate pure and isolated products

As expected, electron-donating groups (**4b** – **4e**) gave excellent yields due to their enhanced nucleophilicity, allowing them to easily react with CS_2 to afford the dithiocarbamate. To our delight, even less nucleophilic anilines were tolerated such as halides (**4f** – **4i**) albeit with slightly lower yields. Remarkably, both the unprotected acid **3j** and ester **3k** gave excellent yields in their isothiocyanates. Terminal alkynes, which are not usually compatible with electrochemical transformations, have shown to remain untouched in our case and afforded the alkyne bearing isothiocyanate **4l** in 44% yield, showing the general applicability of our novel methodology. Finally, remarkably, we were able to prepare **4m** from the easily oxidisable unprotected 4-aminoindole **3m**.

A plausible mechanism for the overall transformation is depicted in Scheme 3. First, the amine attacks CS_2 to form the corresponding dithiocarbamate ammonium salt (DBU-H^+ salt in the case of aniline derivatives). The salt is then oxidised on the anode to generate the corresponding thiocarbamyl cation, which rapidly loses a proton to form the desired isothiocyanate. At the same time, the nickel cathode, having a low hydrogen overpotential, is reducing both ammoniums, regenerating the free amine, and protons present in the solution. The exact mechanism for the desulfurisation step remains unclear. Nevertheless, several possible mechanisms have been postulated in the literature.[11] Cyclic voltammetry (CV) experiments were carried out on octylamine (Figure S3). It shows one single irreversible oxidation event at 1.10V vs $Fc^{+/0}$. Upon titration with CS_2, a second feature at c.a -0.18V vs $Fc^{+/0}$, which we attribute to the oxidation of the octylamine.CS_2 adduct can be observed in addition to the suppression of the original feature. Indeed, when CS_2 was directly added to the octylamine and the resulted solid analysed using cyclic voltammetry, similar features were

observed, confirming the low oxidation feature to be linked to the anodic oxidation of the carbamate salt.

Scheme 3. Proposed mechanism for the isothiocyanation of primary amines



In conclusion, a general, practical, and supporting-electrolyte-free electrochemical approach was developed to prepare isothiocyanates from amines. The novel methodology is mild, and a broad range of functionalised substrates was easily synthesised. Furthermore, the method displays an excellent functional group tolerance in addition to being high yielding.

ASSOCIATED CONTENT

Data Availability

All underlying data available in the article itself and its Supporting Information

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, spectral data, and characterisation of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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