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Catalyst- and Supporting Electrolyte-Free Electrosynthesis of Benzothiazoles and Thiazolopyridines in Continuous Flow

Ana A. Folgueiras-Amador,^{†[a]} Xiang-Yang Qian,^{†[b]} Hai-Chao Xu^{*[b]} and Thomas Wirth^{*[a]}

Abstract: A catalyst- and supporting electrolyte-free method for electrochemical dehydrogenative C–S bond formation in continuous flow has been developed. A broad range of *N*-arylthioamides have been converted to the corresponding benzothiazoles in good to excellent yields and with high current efficiencies. This transformation is achieved using only electricity and laboratory grade solvent, avoiding degassing or the use of inert atmosphere. This work highlights three advantages of electrochemistry in flow, which is (i) a supporting electrolyte-free reaction, (ii) an easy scale-up of the reaction without the need for a larger reactor and, (iii) the important and effective impact of having a good mixing of the reaction mixture, which can be achieved effectively with the use of flow systems. This clearly improves the reported methods for the synthesis of benzothiazoles.

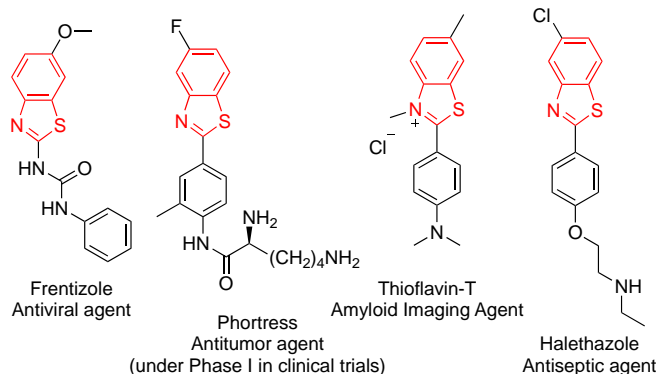
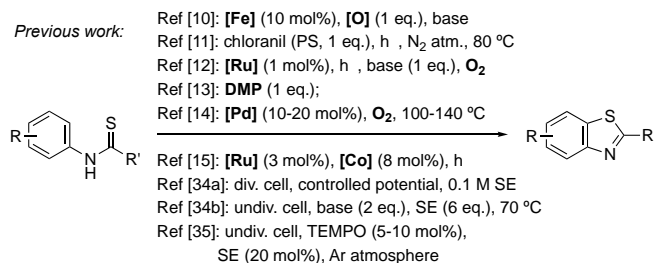


Figure 1. Benzothiazole based clinically available drugs.

Introduction

The formation of carbon-carbon and carbon-heteroatom bonds is one of the most important transformations in organic chemistry. Direct cross-coupling reactions of C–H and X–H (X = heteroatom) have been widely studied in the past due to the simplicity of the method.^[1–5] These methods obviate the need to prefunctionalize the substrate, and thus reduce the number of steps of a synthetic route. Traditional cross-coupling methods frequently use precious transition metals or stoichiometric amounts of organic oxidants, which create waste in the reaction and make large-scale processes difficult.^[6,7] Even if the transition metals are used in catalytic amounts, there is still a need to remove residual metal impurities from the products. The removal of residual metals leads to additional costs.^[8]

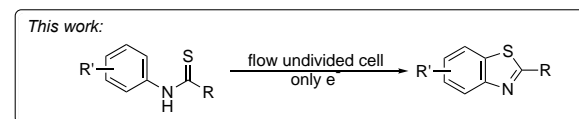
The benzothiazole scaffold is part of a large number of bioactive compounds, including antiviral, antitumor, and antiseptic agents as well as tracers for β -amyloid plaques in Alzheimer disease (Figure 1).^[9] Benzothiazoles can be synthesized by oxidative cyclization of *N*-arylthioamides. These oxidative cyclizations have been achieved using iron-based catalysts,^[10] with chloranil as photosensitizer under irradiation,^[11] or in a combination of visible light, oxygen and ruthenium catalysts and a base.^[12] The major disadvantage of these methods is the undesirable desulfurization of the thioamides to amides as side products. The formation of benzothiazoles from *N*-arylthioamides has also been accomplished by employing hypervalent iodine as the oxidant^[13] and palladium as the catalyst under oxygen atmosphere.^[14] A novel photoredox process employing ruthenium- and cobalt-based catalysts has been recently developed by Wu and Lei, where the use of oxidants is avoided by hydrogen formation from proton reduction.^[15] In spite of all the methods described, the synthesis of 2-alkyl substituted benzothiazoles and thiazolopyridines is still challenging.



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PS = photosensitizer; DMP = Dess-Martin periodinane; SE = supporting electrolyte

Scheme 1. Aromatic dehydrogenative C–S bond formation.

Supporting information for this article is given via a link at the end of the document.

Organic electrochemistry is known as an alternative method to perform redox processes, where toxic or dangerous oxidizing or reducing reagents are replaced by electrons, making such processes more environmentally friendly than traditional methods employing stoichiometric redox reagents.^[16–21] There are a number of examples of electrochemical methods to achieve C–H functionalization.^[22–28] We have recently developed electrochemical reactions to synthesize *N*-heterocycles through creating new C–N bonds,^[29,30] and some of these methods use a mediator such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO)^[31] or ferrocene^[32,33] to perform the oxidation of the substrate.

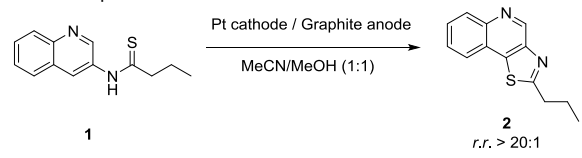
The electrochemistry of benzothiazoles from *N*-arylthioamides was firstly reported in 1979 and lately by Lei.^[34] We have recently developed a versatile method for synthesis of benzothiazoles and thiazolopyridines through mediated electrochemical oxidation of *N*-arylthioamides.^[35] For all of these methods, supporting electrolytes are employed to increase the conductivity of the solution. On the other hand, flow electrochemistry offers many advantages over batch electrochemistry.^[18,36–43] For example, a large ratio of electrode surface to reactor volume reduces the reaction time. In addition, the short distance between electrodes enables a more efficient mass transfer and allows the use of low concentrations of supporting electrolyte or even no supporting electrolyte at all. We have also developed such systems for efficient flow electrolysis.^[44–47] Electrolyte-free solvent systems with a residual conductivity such as acetonitrile/water was recently described by Waldvogel *et al.*,^[48] and provides significant advantages in downstream processing. Herein, we report the first catalyst-free and supporting electrolyte-free electrochemical synthesis of benzothiazoles and thiazolopyridines from *N*-(hetero)arylthioamides using a flow electrochemical reactor.^[47]

Results and Discussion

The cyclization of *N*-(quinolin-3-yl)butanethioamide **1** to thiazolo[4,5-*c*]quinoline **2** was initially studied using reaction conditions similar to those previously employed in batch.^[35] This substrate was chosen because the product **2** (Table 1) was an intermediate in the synthesis of CL075 (a TLR8 receptor agonist).^[49] The electrolysis in flow employed platinum as the cathode, graphite as the anode (working electrode surface: 8.2 cm² each), a solvent mixture of acetonitrile and methanol, and a catalytic amount of TEMPO (5 mol%). Initial reaction optimization used a low current density of 0.49 mA cm⁻² (Table 1, entry 1), and product **2** was obtained in 33% conversion with the consumption of 2 F mol⁻¹ of charge. With a low concentration and flow rate, 6 F mol⁻¹ was needed to achieve full conversion (entry 3). Further experiments showed that TEMPO was not required for the electrolysis of thioamide **1** in flow (entry 4). To increase the throughput, higher flow rates (entries 5 and 6) and substrate concentrations were investigated (entry 7). Under these conditions, similarly high conversions (>99%) were obtained demonstrating that higher production rates can be achieved through increasing the substrate concentration and flow rate. The amount of electricity used in the reaction could be decreased to

2.5 F mol⁻¹ without affecting the conversion (Table 1, entry 8). However, a further reduction to 2.0 F mol⁻¹ led to the drop of the conversion to 90% (Table 1, entry 9). With the optimized conditions (entry 8), a larger scale reaction was performed leading to the formation of the product **2** in 97% isolated yield (121 mg).

Table 1. Optimization of the reaction conditions.



Entry	Concentration [mol L ⁻¹]	Flow rate [mL min ⁻¹]	Current density [mA cm ⁻²]	Current [F mol ⁻¹]	¹ H NMR conversion
1 ^[a]			0.49	2.0	33%
2 ^[a]	0.025	0.05	0.98	4.0	50%
3 ^[a]			1.46	6.0	98%
4		0.05	1.46		>99%
5	0.025	0.1	2.93	6.0	>99%
6		0.2	5.85		>99%
7			11.71	6.0	>99%
8 ^[b]	0.05	0.2	4.88	2.5	>99%
9			3.90	2.0	90%

[a] 5 mol% of TEMPO. [b] 97% isolated yield.

The substrate scope was explored as shown in Table 2 and Figure 2. Results obtained in a batch reactor are provided for comparison. Alkyl and aryl thioamides reacted smoothly with good yields (**3–6**, **9–17**, **20**, **22**). Many functional groups were tolerated in the electrochemical oxidation, such as free alcohols (**14**, **21**), silyl ethers (**15**), esters (**16**, **20**), carbamates (**17**), sulfonamides (**17**, **22**) and phosphine oxides (**24**). The cyclization to benzothiazole could also be obtained with other 2-substituents, such as heteroaryl (**29**) and electron-rich arenes (**6**).

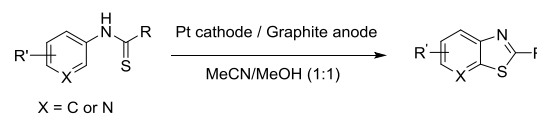


Table 2. Substrate scope.

Product	Flow: Yield [%] (Current [F mol ⁻¹])	Batch: Yield [%] (Current [F mol ⁻¹])

	R ¹ = Ph		
	3 , R ² = H	96 (2.6) ^[a]	95 (3.2)
	4 , R ² = OCF ₃	77 (2.6) ^[a]	92 (3.3)
	5 , R ² = SMe	57 (2.9) ^[a]	68 (4.6)
	6 , R ² = OMe	92 (4.0) ^[a]	90 (3.2)
	R ¹ = <i>n</i> Pr		
	7 , R ² = CN	58 (2.6)	75 (5.6)
	8 , R ² = OMe	70 (2.6)	60 (5.3)
	R ² = H		
	9 , R ¹ = Cy	65 (2.0)	82 (5.6)
	10 , R ¹ = <i>n</i> Bu	81 (2.5)	86 (3.5)
	11 , R ¹ = Bn	64 (4.0)	-
	12 , R = Ph	97 (2.5)	-
	13 , R = <i>n</i> Bu	93 (3.0)	-
	14 , R = OH	66 (2.6)	48 (4.0)
	15 , R = OTBDPS	83 (3.0)	80 (3.5)
	16 , R = CO ₂ <i>t</i> Bu	83 (3.0)	92 (3.9)
	17 , R = TsNBoc	36 (3.0)	56 (4.8)
	18 , R = Ph	81 (3.0)	-
		(<i>r.r.</i> = 19:1)	
	19 , R = <i>n</i> Bu	87 (3.5)	-
		(<i>r.r.</i> = 19:1)	

[a] 3% H₂O was added to the solvent mixture.

TBDPS = *tert*-butyldiphenylsilyl, Ts = 4-toluenesulfonyl, Boc = *tert*-butoxycarbonyl.

Different *N*-aryl groups were also investigated in the electrochemical cyclization. Substrates bearing electron-donating groups (**5**, **6**, **8**, **25**, **27**), electron-withdrawing groups (**4**, **7**, **26**, **28**) and halogens (**23**) underwent successful cyclization. With the same methodology, aminopyridine-derived thioamides were cyclized to thiazolopyridines (**18–21**, **23**). As previously reported, the 3-aminopyridine-derived thioamides showed high regioselectivity for the α -position of the pyridyl ring (**18** and **19**).

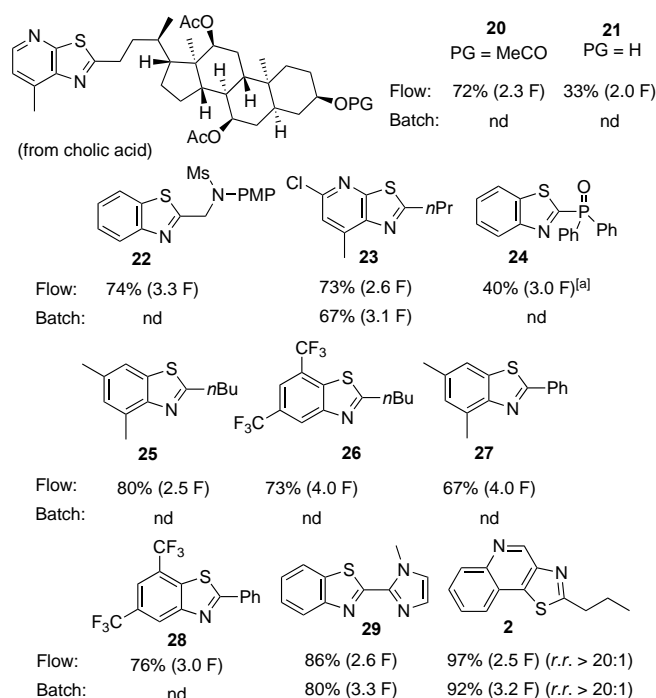
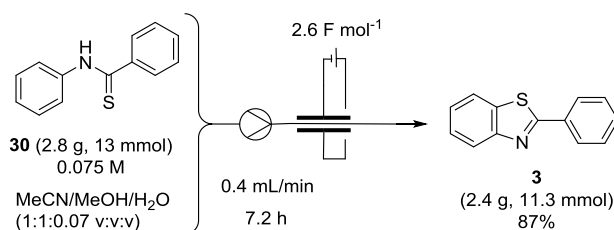


Figure 2. Substrate scope.

[a] 3% H₂O was added to the solvent mixture. nd = not determined, PMP = 4-methoxyphenyl, Ms = methanesulfonyl.

To further demonstrate the synthetic potential of the method herein described, a larger scale reaction (13 mmol) was performed as shown in Scheme 2, using the same flow electrochemical reactor. Compound **3** was obtained in 87% yield (2.4 g). A higher flow rate and higher concentration than the one described in the general procedure were used, which allowed the reaction time to be shortened. This led to a lower yield (87% instead of 96%), but it is still a good sacrifice to obtain a large amount of product in a short time. These results showcased the advantage of flow electrochemistry in reaction scale up. Here the substrate was pumped through the same reactor for a longer time.

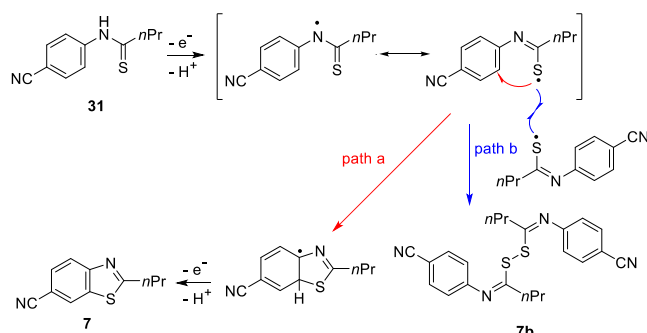


Scheme 2. Large scale benzothiazole synthesis.

When a 2-cyano substituent was attached to the *N*-aryl moiety (**31**), the dimer **7b** was obtained in 13% yield in addition to compound **7**. A similar product has been previously reported in the oxidation of electron-deficient *N*-arylthioamides with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).^[50] To investigate if TEMPO-mediated thioamide oxidation could stabilize the radical

formed and avoid the formation of the dimer **7b**, the oxidation reaction of **31** was performed with catalytic amounts of TEMPO (1 or 10 mol%), but this led to a significant decrease in the conversion of the starting material **31** as the amount of TEMPO was increased. The isolated yields of both benzothiazole **7** and dimer **7b** were not improved by varying the current density (see the Supporting Information for details). The formation of the dimer **7b** pointed to a radical-based mechanism for the formation of the benzothiazoles.

Based on the results described above, a possible mechanism for the electro-synthesis was proposed using thioamide **31** (Scheme 3). The thioamide substrate is oxidized at the anode to form a thioamidyl radical. This radical intermediate can cyclize onto the aryl group to give benzothiazole **7** after rearomatization (path a) and react with a second radical molecule to form the dimer **7** (path b). For most substrates tested in this study, the dimerization product was not observed suggesting the cyclization being predominant in most cases. In our previous manuscript we reported mechanistic investigations of this transformation in batch, and proved that the thioamidyl radical was involved.^[35]



Scheme 3. Proposed reaction mechanism.

Recently, Waldvogel *et al.* reported mechanistic studies of N–N bond formation by dehydrogenative coupling, where two different mechanisms were proposed.^[51] Substrates bearing electron-donating groups having lower oxidation potentials proceed through a cationic intermediate in an oxa-Nazarov-type reaction. A radical pathway is suggested for substrates with electron-donating groups, as their oxidation potential is higher and, after radical formation, a second oxidation to the cation will be more difficult. We performed cyclic voltammetric studies of some of our substrates with electron-rich arenes, and these show two oxidation peaks (see Supporting Information). This result suggests that the electrochemical dehydrogenative C–S bond formation of electron-rich *N*-arylthioamides could involve cationic intermediates, as reported by Waldvogel.^[51]

Conclusions

In conclusion, a novel flow electrochemical method has been developed for the formation of benzothiazoles from *N*-

arylthioamides. In this method, there is no need for any catalyst or supporting electrolyte. An inert atmosphere is also not necessary and laboratory grade solvents can be used without degassing. A gram-scale reaction showed the potential to scale up flow electrochemical processes. This work clearly highlights the advantages of flow electrochemistry and largely improves the reported methods for the formation of benzothiazoles.

Experimental Section

A solution of the thioamide (0.6 mmol) in methanol/acetonitrile (12 mL, 1:1 v/v) was pumped in the electrochemical reactor (0.205 mL inner volume) via syringe pump (0.2 mL min⁻¹), using the corresponding amount of electricity (F mol⁻¹). After reaching the steady state, the solution was collected for 55 min. The solvent was evaporated under reduced pressure, and the crude mixture was purified by flash column chromatography.

Acknowledgements

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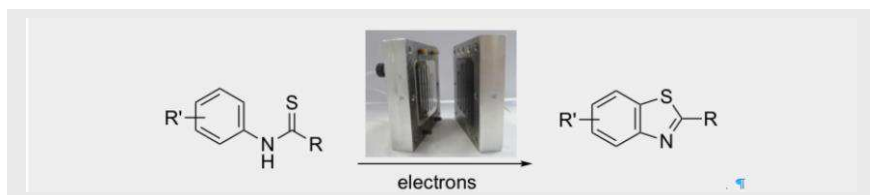
Keywords: flow electro-synthesis • cyclization • supporting electrolyte-free • benzothiazoles

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Entry for the Table of Contents

FULL PAPER



No catalyst and no supporting electrolyte are needed for the formation of benzothiazoles from *N*-aryltioamides. Electrons and a flow reactor for electrochemistry are sufficient.

Ana A. Folgueiras-Amador, Xiang-Yang Qian, Hai-Chao Xu* and Thomas Wirth*

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