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ELECTROOXIDATIVE CYCLIZATION OF BENZYLIDENEAMINOTHIOPHENOLS TO THE CORRESPONDING 2-ARYLBENZOTHAZOLES

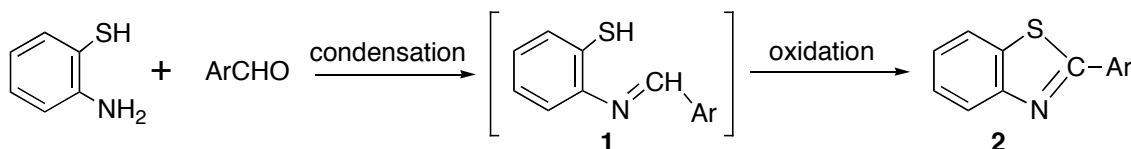
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Abstract – Several benzylideneaminothiophenols were electrochemically oxidized in methanol containing sodium acetate as the supporting electrolyte, to afford the corresponding 2-arylbenzothiazols. The reaction proceeded via intramolecular cyclization involving the formation of a new bond between the benzylic carbon of the substrate and the sulfur of the thiol group. Based on the yields, room temperature and the use of two equivalents of sodium acetate relative to the substrate as the supporting electrolyte were found to be the optimal reaction conditions. The electrooxidation presumably involves a two-electron oxidation process.

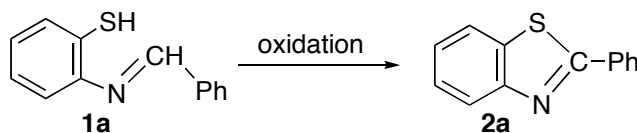
2-Arylbenzothiazoles (**2**) have been proven as remarkably important and useful compounds for, not only industrial, but also pharmaceutical organic synthesis, especially as antitumor agents.¹ Among the various methods for preparing the 2-arylbenzothiazole nucleus,² a popular route involves the oxidative cyclization of a benzylideneaminothiophenol (**1**), which can be readily formed *in-situ* as an intermediate by the condensation of equimolar amounts of aminothiophenol and an aromatic aldehyde (Scheme 1).³



Scheme 1 Formation of 2-Arylbenzothiazols

Alternatively, as our continuous study, we have reported on the oxidative cyclization via electrochemical oxidation of various nitrogen-containing substrates.⁴ In recent years, much attention have been given to the unique and efficient strategy of organic synthesis involving electrochemical methods due to: 1) environment friendly reaction conditions, 2) ease of control of the reaction, 3) ability to access uncommon reactions that are challenging via chemical reagent, and 4) very mild reaction conditions.⁵ Herein, we report on successful application of the electrochemical technique for the effective electrooxidative cyclization of benzylideneaminothiophenols into the corresponding 2-arylbenzothiazoles, which, to the best of our knowledge, has yet to be reported.

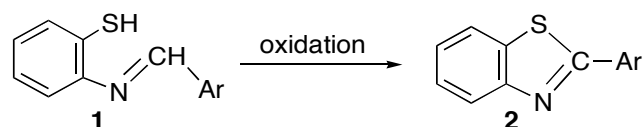
To determine the optimal reaction conditions, electrooxidations were carried out using a model substrate, 2-(benzylideneamino)benzenethiol (**1a**), into the corresponding fused-ring heterocyclic compound, 2-phenylbenzothiazole (**2a**). Using various supporting electrolytes, as listed in Table 1, the electrooxidation reactions revealed significant differences in the yields of the product. In the cases of basic supporting electrolytes such as NaCN (Run 8), NaOH (Run 9), and NaOMe (Run 10), the yields were 40%, 48%, and 36%, respectively. Higher yields were obtained by using neutral salts such as NaClO₄ (Run 1) 62%, LiClO₄ (Run 2) 74%, and *p*-TsON(ET)₄ (Run 3) 69%. Halide ion sources such as KI (Run 4) 30% and KBr (Run 5) 72%, which can often act as mediator (indirect electrooxidation), did not exhibit any significant effects on the yields.⁶ In the cases of low yields, the starting material was recovered and/or considerable amounts of an unidentified tar-like material was formed. A maximum yield of 82% was obtained when 20 mmol of NaOAc was used (Run 7). In a separate study, reactions (using 10 mmol substrate) showed that the amount of NaOAc (5, 10, 20, and 30 mmol) affected the yield of the product (72%, 76%, 82%, and 77%, respectively). Moreover, preliminary electrooxidations studies revealed that amount of the charge passed (0.5, 1.0, and 1.5 F mol⁻¹) increased the formation of **2a** proportionally (25%, 47%, and 62%, respectively). The maximum yield of 82% was obtained after passage of 2.1 F mol⁻¹ (*ca.* 110 min); whereas, excessive passage (3.0 F mol⁻¹) caused a decrease in the yield (70%).

Table 1 Electrochemical cyclization of 2-(benzylideneamino)benzenethiol^a

Runs	Supporting electrolytes	mmol	Recovery of 1a	Yield of 2a
			(%) ^b	(%) ^b
1	NaClO ₄	10	2	62
2	LiClO ₄	10	13	74
3	<i>p</i> -TsON(Et) ₄	5	6	69
4	KI	10	44	30
5	KBr	10	0	72
6	NaOAc	10	5	76
7	NaOAc	20	0	82
8	NaCN	10	10	40
9	NaOH	10	32	48
10	NaOMe	10	12	36
11	NaOMe + KI	5 + 5	36	28

^aSubstrate **1**: 10 mmol, MeOH: 40 mL, Current passed: 2.1 F mol⁻¹, Constant current: 0.3 A, rt: *ca* 15 °C, Anode: Pt, Cathode: Ni. ^b Determined by GC analysis.

Based on the above observations, electrooxidations were subsequently carried out using various benzylideneaminothiophenols (**1a-1k**) to form the corresponding 2-arylbenzothiazols (**2a-2k**). For each electrooxidation, the composition of the anolyte was monitored using GC or TLC – when the substrate was deemed as almost completely consumed, the DC power supply was switched off.

Table 2 Electrochemical cyclization of benzyldeneaminothiophenols ^a

Substrate	Ar	Current passed	Mp (°C)		Yield of 2a-2k
		(F mol ⁻¹)	Obs.	Lit.	(%) ^c
1a	Ph	2.10	109-111	113 ^{2(a)}	69
1b	<i>p</i> -Me-C ₆ H ₄	2.24	82-83	85 ^{3(b)}	70
1c	<i>o</i> -Me-C ₆ H ₄	2.24	55-57	53-54 ^{3(b)}	80
1d	<i>p</i> -MeO-C ₆ H ₄ ^b	2.15	119-120	119-121 ^{2(a)}	71
1e	<i>p</i> -Cl-C ₆ H ₄ ^b	2.06	115-117	117-118 ^{3(b)}	68
1f	<i>o</i> -Cl-C ₆ H ₄	2.23	80-82	81-82 ^{3(b)}	72
1g	<i>p</i> -NO ₂ -C ₆ H ₄ ^b	2.15	224-226	229-230 ^{2(a)}	81
1h	<i>o</i> -NO ₂ -C ₆ H ₄ ^b	2.15	123-125	127-128 ^{3(b)}	63
1i	<i>p</i> - <i>tert</i> -Bu-C ₆ H ₄	2.24	105-107	107-108 ^{2(d)}	74
1j	2-pyridyl	2.15	130-132	129-130 ^{3(h)}	82
1k	3-pyridyl	2.15	125-127	-	83

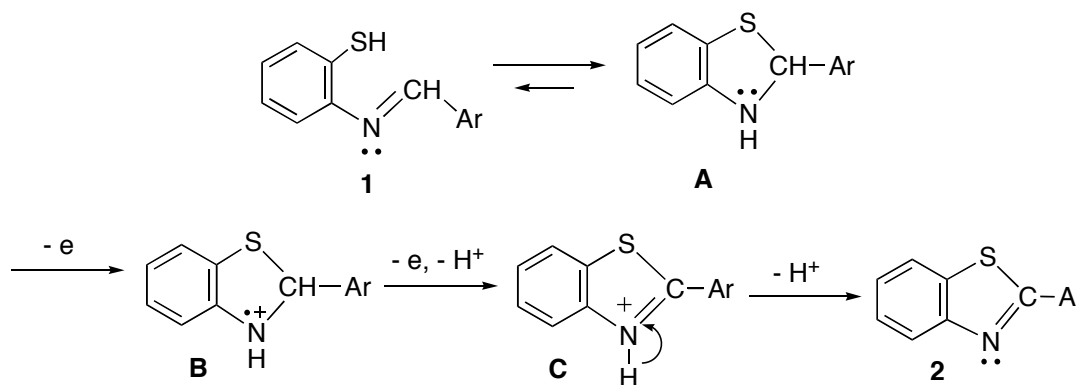
^aSubstrate **1**: 10 mmol, NaOAc: 20 mmol, MeOH: 40 mL, rt: *ca* 15 °C, Anode: Pt, Cathode: Ni.

^b Mixture of MeOH (25 mL) and acetone (15 mL) was used as the solvent. ^c Isolated yield.

As listed in Table 2, 2-arylbenzothiazols **2a-2k** were obtained in moderate to good yields by passing 2.06 to 2.24 F mol⁻¹ of electricity. The nature of the substituents on the phenyl group did not show significant effects on the yield of the products. Unexpectedly, in the cases of **1d**, **1e**, **1g**, and **1h**, the reactions under the same reaction conditions as **1a** did not give satisfactory yields – moreover, during the course of the electrooxidations, the surface of the anode was gradually covered with a dark-brown tar-like material that was difficult to dissolve in methanol. Upon further investigations, the yield of the product was improved by the addition of acetone (methanol, 25 mL and acetone, 15 mL) – for example, in the case of

1d, the yield of **2d** increased from 46% to 71% by modifying the solvent.

Although experiments that illustrate the reaction mechanism have not been carried out, a possible mechanism (as shown in Scheme 2) can be described as follow: first, substrate **1** would exist in equilibrium with **A**,^{3(e)} which can lose one electron from the lone electron pair on the nitrogen atom to the anode to form cation radical **B**. The radical would immediately undergo deprotonation and a one-electron oxidation to give iminium ion **C**, which would then undergo deprotonation of the nitrogen atom to produce the desired cyclization product **2**. In this scheme, NaOAc would serve as the appropriate base to facilitate the deprotonation of both cation radical **B** and iminium ion **C**. Overall, substrate **1** would lose two protons and two electrons during the course of the reaction to form **2**. It is interesting to note that the reaction is analogous to the dehydrogenations of benzyl-type amines that were reported in our previous work.⁷



Scheme 2 Proposed scheme of the oxidative cyclization

In conclusion, we have been shown a novel method toward the synthesis of various 2-arylbenzothiazoles via electrooxidation of benzylideneaminothiophenols. Although the yields are moderate to good, our methodology possess the following benefits: 1) the reaction does not require any oxidants and/or special reagents, 2) the reaction can be carried out at room temperature, and 3) the substrates are readily available, 4) the reaction involves a simple, one-pot procedure. Further investigations on the preparation of products having a similar nucleus, such as 2-arylbenzoxazoles and 2-arylbenzimidazoles from the corresponding Schiff base are currently underway in our laboratories.⁸

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General procedures: Benzylideneaminothiophenols were prepared via typical condensation of aminothiophenol and the corresponding aromatic aldehydes in ethanol at room temperature. Melting points of the products were in good agreement with those of the authentic samples. New compound (product **2k**) was characterized by IR, mass, and NMR spectroscopy. Preparative-scale electrooxidations were carried out in a tall 50-mL beaker equipped with a fine frit cup (porosity, *ca.* 100 μ m) as the cathode compartment with a nickel coil (diameter, 0.8 mm; length, 250 mm) as the cathode, and an insert cylindrical platinum net (diameter, 32 mm; height, 35 mm; 55 mesh) as the anode. Electrooxidations of the substrates were carried out as follow: a solution of the substrate (**1a-1k**, 10 mmol) and NaOAc (1.64 g, 20 mmol) in MeOH (40 mL) or MeOH/acetone (25 mL / 15 mL) was electrooxidized under a constant current (0.3 A). During the course of the electrooxidation, the anolyte was magnetically stirred while the temperature of the cell was maintained between 15 and 20 °C. Upon passage of electricity, if the anode was covered with product, it was washed with CHCl_3 . The reaction mixture was concentrated *in vacuo* at approximately 50 °C to remove most of the solvent. Subsequently, the residue was treated with

water (*ca.* 40 mL), and the resulting solid material was extracted using Et₂O or CHCl₃ (3 x 60 mL), which were combined, and dried over magnesium sulfate. After the removal of the solvent, the residue was purified by silica gel column chromatography (diameter, 30 mm; length, 600 mm) using CHCl₃ or a mixture of EtOAc and hexane (1 : 9) as the elution solvent.