SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 18, pp. 3343–3348, 2004

Nickel-Catalyzed Electrochemical Synthesis of Dihydro-Benzo[b]thiophene Derivatives#

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ABSTRACT

The intramolecular electrochemical reductive cyclization of *ortho*-haloaryl allyl thioethers catalyzed by Ni(II) complexes associated to cyclam ligands affords dihydro-benzo[b]thiophene derivatives in moderate to good yields.

Key Words: Benzothiophene; Nickel; Electrochemical; Cyclization; Allyl aryl sulfide.

#Dedicated to Pr. E. Dinjus for its 60th anniversary.

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DOI: 10.1081/SCC-200030579 0039-7911 (Print); 1532-2432 (Online)
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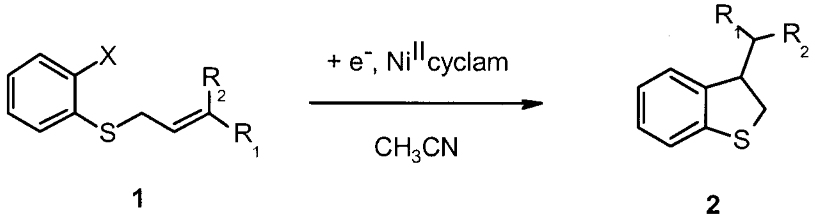
Benzo[b]thiophene structures are interesting molecules, in particular because of their pharmacological properties; some of the derivatives are known to present antifungic, antimycotic, and analgesic activities.[1] The chemical preparation of benzo[b]thiophene derivatives has been reported via a radical-type cyclization in the presence of stoichiometric amounts of tributyltin hydride and AIBN from halogenated aryl thioallyl compounds, in particular with aryl-iodide derivatives.[2,3] Pd(0)-catalyzed intramolecular cyclization of allyl *o*-iodophenyl sulfides in an Heck-type reaction may also afford related benzo[b]thiophene derivatives in good yields.[4]

Electrochemistry, associated with organometallic catalysis, may constitute an alternative catalytic approach to these cyclization reactions. Thus, the selective cyclization of halides on unsaturated C–C bond has been reported in an electrochemical Ni(II)-catalyzed reaction.[5] The process was highly dependent on the nature of the ligand associated to metal center.[6] Ni(II) complexes associated with tetraaza macrocyclic ligands such as cyclam (1,4,8,11-tetraazacyclotetradecane) were able to efficiently catalyze the intramolecular cyclization.

In the present study, we report on the use of the electrochemical method for the Ni(II)-catalyzed preparation of dihydrobenzo[b]thiophene derivatives of type **2** starting from *ortho*-haloaryl allyl thioethers **1** (Sch. 1).



	X	R_1, R_2
1a	Br	H, H
1b	Cl	H, H
1c	Br	Me, H
1d	Br	Me, Me
1e	Br	Ph, H

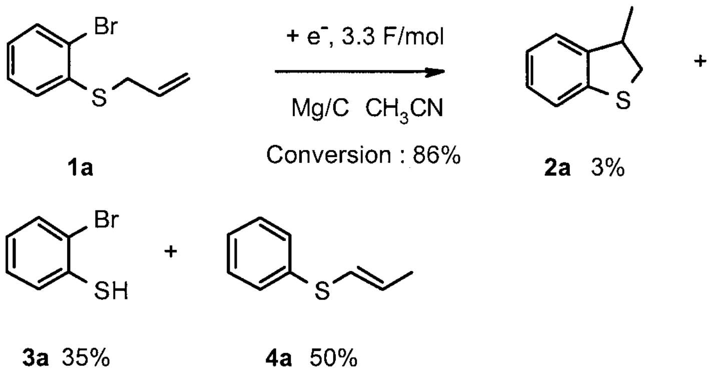
Scheme 1.

The electrochemical method was based on the use of a one-compartment cell fitted with a sacrificial metal anode (generally magnesium) and a concentric carbon fibre cathode.[7] The reactions were conducted in acetonitrile at constant current density of 0.1 A/dm^2 (constant current of 60 mA), at room temperature, with 10 mol% catalyst with respect to the starting *ortho*-haloaryl allyl thioethers **1**. Allyl thioethers **1** were prepared from *ortho*-chloro or bromo thiophenols and the corresponding allyl chlorides or bromides in DMF, in the presence of K_2CO_3 at 50°C, with yields in the range of 64% to 95%.

When the bromo derivative **1a** was electrolyzed in acetonitrile without any catalyst in the presence of a Mg anode and a carbon fibre cathode, a non-selective mixture of compounds **2a**–**4a** was formed in 86% conversion after 3.3 F/mol. The desired cyclized product, 3-methyl-2,3-dihydrobenzo[b]thiophene **2a**, was obtained in only 3% yield. 2-Bromothiophenol **3a**, issued from the cleavage of the S-C(allyl) bond, was formed in 35% yield, and **4a** issued from the double-bond isomerization and the cleavage of the aryl-bromide bond was obtained in 50% yield (Sch. 2).

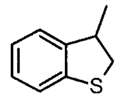
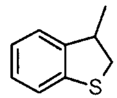
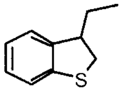
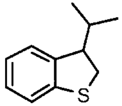
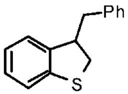
The same reaction in the presence of a catalytic amount of Ni(cyclam)Br_2 as the catalyst (10 mol%) allowed the chemoselectivity toward the cyclized compound **2a** to improve to 39%. Under these conditions, **3a** and **4a** were formed in 39% and 18% yields, respectively.

The nature of the solvent was also examined. Thus, when the Ni(cyclam)Br_2-catalyzed reaction of **1a** was run in DMF instead of acetonitrile, the cyclic compound **2a** was formed in 25% yield. Acetonitrile was therefore the solvent of choice for further electrolyses.



Scheme 2.

Table 1. Electrolysis of *ortho*-haloaryl allyl thioethers **1a**–**1e** in the presence of Ni(cyclam)$(BF_4)_2$ as the catalyst (10 mol%).

Entry	Substrate	Consumption	Benzo[b]thiophene (%yield)[a]			^1H NMR ($CDCl_3$) and mass spectra (70 eV) of **2**
1	**1a**	95%		**2a**	(73)	^1H NMR: 7.3–7.0 (4H, m); 3.5–3.4 ($2H_2$, m); 3.1–2.9 ($1H_3$, m); 1.4 (3H, d, 6 Hz). MS: 150(M^+), 135, 115(100%), 91
2	**1b**	78%		**2a**	(40)	
3	**1c**	75%		**2c**	(60)	^1H NMR: 3.5–3.4 ($1H_2$, m); 3.1–2.9 ($1H_2$, m); 1,9–1,8 (1H, m); 1.1–1.3 (2H, m); 0.9 (3H, d, 7.4 Hz). MS: 164(M^+), 135 (100%), 91
4	**1d**	78%		**2d**	(64)	^1H NMR: 7.3–7.0 (4H, m), 3.6–3.3 ($2H_2$, m); 2.4–2.2 ($1H_3$, m); 1.1 (3H, d, 5 Hz); 0.8 (3H, d, 5 Hz). MS: 178 (M^+), 135(100%), 91
5	**1e**	75%	 	**2e**	(59)	^1H NMR: 7.3–7.0 (9H, m); 3.7–3.6 ($1H_2$, m); 3.5–3.4($1H_2$, m); 3.2- 3.0 (2H, m); 2.7 (1H, m). MS: 226 (M^+), 135 (100%), 91

[a] General electrolysis conditions: Distilled acetonitrile (30 mL) is introduced in a one-compartment cell fitted with a Mg rod anode and a carbon fiber cathode, together with Bu_4NBF_4 (1 mM), [Ni(cyclam)$(BF_4)_2$] (0.2 mmol), and substrate **1** (2 mmol). The solution is stirred and electrolyzed at constant current of 60 mA (5–15 V between the electrodes), for 3 hr. The solution is then hydrolyzed with HCl (0.1 M) and extracted with Et_2O. The organic layers were dried with $MgSO_4$ and then filtered off and evaporated. The products were analyzed by ^1H and ^{13}C-NMR and mass spectrometry. Isolated yields are based on the converted starting thioether after 3.3 F/mol.

A further improvement in the selectivity toward **2a** could be achieved by using Ni(cyclam)$(BF_4)_2$ as the catalyst. The electrolysis of **1a** with 10 mol% of Ni(cyclam)$(BF_4)_2$ in acetonitrile with Mg/C as the couple of electrodes led to cyclic **2a** in 73% yield.

The influence of the anodic and cathodic materials was examined in reactions of **1a** [with Ni(cyclam)$(BF_4]_2$ as the catalyst in acetonitrile). The use of either aluminum or zinc rods as the anodes, combined with a carbon fiber cathode, led to yields of **2a** of 40% and 51%, respectively, and did not allow the yield of cyclized compound obtained with a magnesium anode to further improve. By using stainless steel instead of carbon fiber as the cathode (with a magnesium anode), the cyclization process of **1a** was completely inhibited and the isomerization reaction leading to **4a** became the predominant process.

The best electrolytic conditions (see Table 1) were extended to the cyclization of a series of *ortho*-haloaryl allyl thioethers **1a**–**1e**. Table 1 summarizes these results.

Whereas the intramolecular cyclization of *ortho*-bromoaryl allyl thioether **1a** afforded 73% yield of 3-methyl-2,3-dihydrobenzo[b]thiophene **2a** with 95% conversion after 3.3 F/mol (entry 1), the corresponding chloride derivative **1b** (entry 2) led only to 40% of 3-methyl-2,3-dihydrobenzo[b]thiophene. Although moderate, this result is interesting because the activation of the aryl-chlorine bond is more difficult than that of the Ar-Br bond, and the possibility to get cyclization to **2a** from the chloride derivative has not yet been reported with the more classical stoichiometric chemical procedures, which generally need the more activated iodo (or sometimes bromo) derivatives.[2,3] In the electrochemical cyclization of **1b**, the main by-product was the cleavage compound **3b** (Sch. 2), obtained with 46% yield.

Entries 3–5 involved the cyclization of alkyl-substituted allyl thioethers **1c**–**1e**. With substrate consumptions of 75% to 78%, the yields of the expected cyclic products **2c**–**2e** were in the range of 59% to 64%.

In conclusion, a series of dihydrobenzo[b]thiophene derivatives could be prepared from *ortho*-haloaryl allyl thioethers by using an electrochemical method, which allows a catalytic intramolecular reductive cyclization of these derivatives assisted by nickel complexes. The electrochemical process is of very simple set-up and makes it possible to obtain moderate to good yields of cyclized compounds, even starting from aryl chloride derivatives.

REFERENCES

1. (a) Al Nakib, T.; Meegan, M.J.; Looney, A.M.; Burke, M.L. Eur. J. Med. Chem. **1992**, *27* (9), 971–976; (b) Katritzky, A.R.; Fali, C.N.; Li, J.

J. Org. Chem. **1997**, *62*, 8205–8209; (c) Chen, S. PCT Int. Appl., WO 2003075943, 2003; 57.
2. Ko, C.-W.; Chou, T.-S. J. Org. Chem. **1998**, *63* (14), 4645–4653.
3. Chen, M.-H.; Abraham, J.A. Tetrahedron Lett. **1996**, *37* (30), 5233–5234.
4. Arnau, N.; Moreno-Mañas, M.; Pleixats, R. Tetrahedron **1993**, *49* (47), 11019–11028.
5. (a) Ozaki, S.; Horiguchi, I.; Matsushita, H.; Ohmori, H. Tetrahedron Lett. **1994**, *35*, 725–728; (b) Mubarak, M.S.; Peters, D.G. J. Electroanal. Chem. **1992**, *332*, 127–134; (c) Olivero, S.; Rolland, J.-P.; Duñach, E. Organometallics **1998**, *17*, 3747–3753; (d) Dunach, E.; Esteves, A.P.; Freitas, A.M.; Lemos, M.A.; Medeiros, M.J.; Olivero, S. Pure & Applied Chem. **2001**, *73*, 1941–1945.
6. Olivero, S.; Duñach, E. Synlett **1994**, *7*, 531–533.
7. (a) Sock, O.; Troupel, M.; Périchon, J. Tetrahedron Lett. **1985**, 1509–1512; (b) Silvestri, G.; Gambino, S.; Filardo, G.; Greco, G.; Gulotta, A. Tetrahedron Lett. **1984**, *25*, 4307–4308.

Received in the UK April 21, 2004