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Two birds with one stone: redox co-production of 2-arylbenzothiazoles and hydroquinone

Guiyun Li · Yanqing Peng

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Abstract A variety of 2-arylbenzothiazoles are co-produced with hydroquinone in the absence of additional reagents and catalysts under mild conditions. When this inherently waste-free process is employed, none of the reactions require the use of additional redox reagents, and all of them are environmentally friendly with excellent atom economy (≥95%).

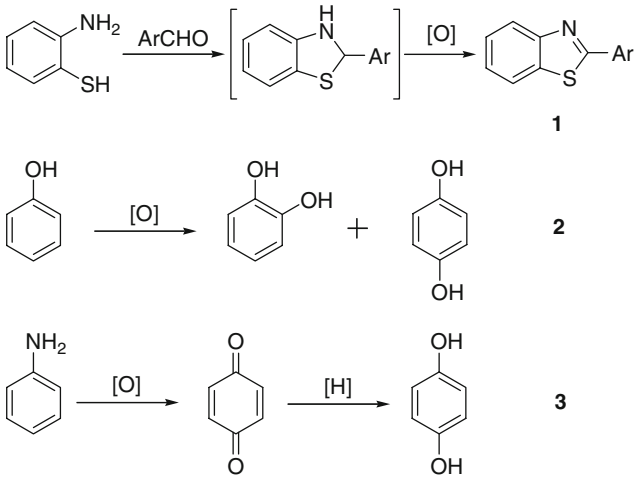
Keywords Green chemistry · Atom economy · Oxidations · Reductions

Introduction

The benzothiazolyl moiety is a structural element of compounds with potent and selective antitumour activity [1], of wide-spectrum Ca(II) channel antagonists [2], and of inhibitors of several enzymes [3]. Typically, 2-arylbenzothiazole is synthesized from 2-aminobenzenethiol and aromatic aldehydes through a benzothiazoline intermediate. The benzothiazoline is then aromatized by oxygen or hydrogen peroxide in the presence of a catalytic amount of Lewis acid to give the desired 2-arylbenzothiazole (Scheme 1, **1**) [4]. Very recently, TEMPO has been found to be an efficient organocatalyst for the aerobic oxidative synthesis of 2-substituted benzothiazoles [5]. On the other hand, hydroquinone is an important chemical employed as an antioxidant, photographic developer and polymerization inhibitor, and it can be used as a starting material in the synthesis of resins, dyes, and pharmaceuticals. Phenol hydroxylation using hydrogen peroxide is a useful method of making catechol and hydroquinone (Scheme 1, **2**) [6]. Unfortunately, to date, the conversion reported in the literature for phenol to dihydroxybenzenes is relatively low. In most actual industrial processes (especially in developing countries), hydroquinone is obtained from the catalytic hydrogenation of 1,4-benzoquinone. Transition metal-based oxidants such as manganese and chromium salts are often used for the oxidation of aniline to benzoquinone [7], but the main drawbacks of these reagents are their negative effects on the environment and the difficulties associated with the recovery and regeneration processes (Scheme 1, **3**). In the recent literature [8], 1,4-benzoquinone was also obtained as a by-product in the hydroxylation of benzene under air and carbon monoxide, as catalyzed by $H_7PMo_8V_4O_{40}$.

One aim of green chemistry is to decrease or eliminate by-products and/or wastes before they are produced. Manufacturing two chemicals in one process presents an interesting challenge to the ingenuity of chemists and chemical engineers. The first milestone in this co-production approach occurred in the early 1950s, when phenol and acetone were synthesized simultaneously [9]. In the Hercules process, cumene produced from the Friedel–Crafts alkylation of benzene by propylene was oxidized, and the corresponding hydroperoxide thus obtained was then cleaved with diluted H_2SO_4 to provide phenol and acetone. Some new procedures have recently been established that are based on co-production strategies. The treatment of CCl_4 over supported Pd or Pt catalysts in the presence of ethanol gives not only the selective synthesis of chloroform but also the conversion of ethanol to diethyl carbonate and 1,1-diethoxyethane [10]. Palladium/phosphine-catalyzed

G. Li · Y. Peng (✉)
Shanghai Key Laboratory of Chemical Biology,
Institute of Pesticides and Pharmaceuticals,
East China University of Science and Technology,
Shanghai 200237, People's Republic of China
e-mail: yqpeng@ecust.edu.cn



Scheme 1

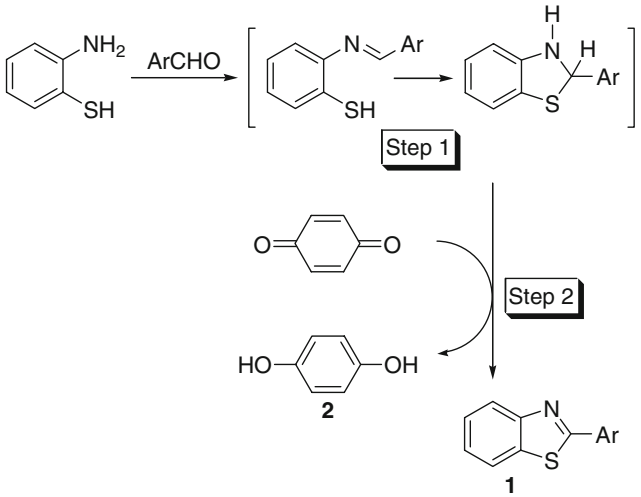
chloroarene C–Cl bond activation provides an efficient method for the selective oxidation of alcohols and the hydrodechlorination of chloroarenes [11]. The coupling of the dehydrogenation of cyclohexanol and the hydrogenation of furfural has been studied for the production of cyclohexanone and 2-methylfuran [12]. In a similar process, maleic anhydride hydrogenation and cyclohexanol dehydrogenation have also been combined for the simultaneous synthesis of butyrolactone and cyclohexanone [13].

In this paper, we wish to report a novel protocol by which 2-arylbenzothiazoles and hydroquinone are co-produced in one reaction sequence. The basic idea here was to synthesize 2-arylbenzothiazoles and hydroquinone simultaneously through the redox reaction between 2-aryl-2,3-dihydrobenzothiazoles (as hydrogen donor) formed in situ and 1,4-benzoquinone. There are obvious economic and environmental advantages to this approach, such as atom economy, lower energy consumption, and less waste disposal.

Results and discussion

This reaction is rationalized as follows. Firstly, hydrogen-donating 2-aryl-2,3-dihydrobenzothiazole (benzothiazoline) [14] is formed by the condensation of various aromatic aldehydes and 2-aminobenzenethiol. Secondly, the benzothiazoline is aromatized successively through hydrogen transfer with 1,4-benzoquinone to give 2-arylbenzothiazole and hydroquinone (Scheme 2).

As a starting point for the development of our co-production methodology, various reaction conditions such as solvents, atmosphere, feed-in fashion of reactant, and temperature were examined using benzaldehyde, 2-aminothiophenol, and 1,4-benzoquinone (Table 1, entry 1) as model substrates.



Ar = C_6H_5-, 4-CH_3O-C_6H_4-, 4-CH_3-C_6H_4-, 4-Cl-C_6H_4-, 3-Br-C_6H_4-, 3-NO_2-C_6H_4-, 4-OH-C_6H_4-

Scheme 2

Table 1 Redox co-production of 2-arylbenzothiazoles and hydroquinone

Entry	Time (h)[a]	Ar	Yield **1** (%)[b]	Yield **2** (%)[b]
1	1 + 0.5	C_6H_5	94	90
2	1 + 1	4-CH_3O–C_6H_4	93	92
3	1 + 1	4-Cl–C_6H_4	90	94
4	1 + 1	4-CH_3–C_6H_4	98	95
5	1 + 1	3-Br–C_6H_4	98	82
6	1 + 1	3-NO_2–C_6H_4	95	76
7	1 + 1	4-OH–C_6H_4	96	85

[a] Reaction time of two steps

[b] Isolated yields

The choice of solvent plays a very important role in these reactions. It was found that the reaction occurred rapidly in polar protic solvents such as methanol and ethanol. They did not make a definitive difference in the first step (cyclization) according to the reaction rates and conversions. In the second step (hydrogen transfer), unidentified by-products were unfortunately detected in the cases using methanol as solvent. In contrast, the use of less polar solvents (e.g. CH_2Cl_2 and THF) as well as polar aprotic solvents (e.g. acetonitrile, DMSO, and NMP) led to prolonged reaction times and low yields. Based on these results, ethanol was then selected as the solvent of choice for further investigations. The influence of the temperature on the model reaction was also checked. Excellent yields were obtained in cases performed at room temperature. Running the reaction at elevated temperature resulted in a prominent decrease in the yield due to side reactions.

The feed-in fashion of the reactants affects the reaction results to a certain extent. In the first step of the reaction

sequence, if one reactant was mixed with another in one portion (either neat or in solution), the mixture turned brown rapidly and was accompanied by apparent exothermicity. When aldehyde in ethanol was added dropwise to an alcoholic solution of aminothiophenol, the cyclization proceeded smoothly and no by-products could be detected by TLC. In comparison, the second step of the reaction is insensitive to feed-in fashion; therefore, 1,4-benzoquinone could be added in one portion. An attempt to add three starting materials (aldehyde, aminothiophenol, and benzoquinone) in one portion failed completely. Only traces of the expected products were found, along with large amounts of by-products.

Recently, the application of Hantzsch 1,4-dihydropyridine as reductant (hydrogen donor) has been a hot topic in organic synthesis [15]. In many cases where Hantzsch 1,4-dihydropyridine and other NAD(P)H analogues such as 1-benzyl-1,4-dihydronicotinamide [16] were used, it was emphasized that the transfer hydrogenation reactions were performed under an argon or nitrogen atmosphere. To explore the effect of atmosphere on our reaction couple, control experiments were conducted under both an ambient and a nitrogen atmosphere. It is worth noting that, at the end of the first step of the reaction, a small amount of 2-arylbenzothiazole could be detected along with 2-aryl-2, 3-dihydrobenzothiazole, perhaps due to the aerobic oxidation of the desired compound under an ambient atmosphere. Hence, protection from oxygen is necessary for higher final yields.

After optimizing the abovementioned reaction conditions, the following protocol was subsequently used. Aromatic aldehydes were treated with 2-aminothiophenol (1 equiv.) followed by 1,4-benzoquinone (1 equiv.) at room temperature in ethanol under a nitrogen atmosphere for 1.5–2 h. Under these conditions, a number of redox sequences occurred that gave the corresponding benzothiazoles and hydroquinone with high yields and chemoselectivities (Table 1). Substituent effects of aromatic terminal alkynes and aromatic iodides were also examined. The results indicate that the reaction is relatively insensitive to the electronic characteristics of a substituent as well as its location.

One of the principles of green chemistry is to employ catalysts instead of stoichiometric reagents. In the present method, neither a stoichiometric reagent nor a catalyst is necessary to obtain two useful products in one reaction sequence. In other words, since no reagent is used in this process, waste disposal becomes easier. Energy requirements have environmental and economic impacts and should be minimized for cleaner processing. By all appearances, our two-in-one transformation accords with the above requirements in several respects, such as simplified work-up procedure and room temperature manipulations. From the viewpoint of atom economy [17], co-production processes would be highly beneficial. When our procedure was employed, in the case of 2-phenylbenzothiazole and hydroquinone synthesis (Table 1, entry 1), the theoretical atom economy was calculated as 95%. Only one water molecule was eliminated during the imine formation step, and the hydrogen transfer step has 100% atom economy.

The ease of separation of the two products is an important issue in evaluating a potential co-production process. In our procedure, the two products could be readily separated by water dilution. Hydroquinone was isolated from 2-arylbenzothiazoles due to its excellent solubility in aqueous ethanol (50 wt%). In contrast, at room temperature, the solubility of 2-arylbenzothiazoles in aqueous ethanol (50 wt%) is very poor.

In summary, a novel and practical approach to 2-arylbenzothiazoles and hydroquinone was developed based on the redox co-production strategy. The waste stream minimization, operational simplicity, good energy efficiency, atom economy, excellent yields, and the straightforward nature of the reaction procedure make it a very useful addition to the toolbox of organic chemists and chemical engineers.

Experimental

All products are known compounds; their physical and spectroscopic data were compared with those reported in the literature [18–21] and found to be identical. Melting points were measured on a Büchi B-540 apparatus. IR spectra were recorded on a Nicolet Nexus 470 spectrophotometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker AV 400 spectrometer in $CDCl_3$ with TMS as internal standard.

General procedure: redox co-production of 2-arylbenzothiazoles and hydroquinone

To a magnetically stirred solution of 0.63 g of 2-aminothiophenol (5 mmol) in 5 cm^3 ethanol was added, in a dropwise fashion over 5 min, 5 mmol of aromatic aldehyde dissolved in 5 cm^3 of ethanol. The mixture was stirred at room temperature until the starting reactants were completely consumed (monitored by TLC). Then 0.54 g of 1,4-benzoquinone (5 mmol) were added in one portion. The color of the mixture turned dark red within 5 min, and gradually faded to colorless as the reaction proceeded (0.5–1 h). On completion, approximately 5 cm^3 of solvent were removed by rotary evaporation, and the residual reaction mixture was diluted with 4 cm^3 of water. The precipitates thus formed were collected by filtration and recystallized from 95% aqueous ethanol to afford 2-

arylbenzothiazoles in excellent yields. The filtrate containing 1,4-benzoquinone was then evaporated to dryness. Recrystallization of the solid residue from EtOH–CH_2Cl_2 (1:1) gave pure 1,4-benzoquinone as white or pink powders.

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