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An efficient electrochemical method for the atom economical synthesis of some benzoxazole derivatives†

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Electrochemical synthesis of some 2-arylbenzoxazoles were directly carried out *via* the electrochemical oxidation of 3,5-di-*tert*-butylcatechol in the presence of benzylamines without using any catalyst under mild and green conditions. The results show that electrogenerated 3,5-di-*tert*-butyl-1,2-benzoquinone participates in the reaction with benzylamine derivatives and, *via* the *ECCE* mechanism "electron transfer + chemical reaction (imine formation) + chemical reaction (cyclization) + electron transfer", converts to the corresponding benzoxazole derivatives. In this work, some benzoxazole derivatives with high yields in aqueous solutions, without toxic reagents and solvents at a carbon electrode using an environmentally friendly novel method, are provided.

Introduction

Benzoxazole and its derivatives as heteroaromatic systems are important structural motifs in many biologically active natural products and pharmaceutical compounds.[1] These compounds are used as cytotoxic agents,[2] cathepsin S inhibitors,[3] HIV reverse transcriptase inhibitors,[4] estrogen receptor agonists,[5] selective peroxisome proliferator activated receptor antagonists,[6] anticancer agents,[7] and orexin-1 receptor antagonists.[8] They have also found application as herbicides and fluorescent whitening agent dyes.[9] Due to the importance of these compounds as components in pharmaceutical agents, a great deal of effort has been devoted to the synthesis of the benzoxazole derivatives. There are several common methods which have been used, including: (a) metal catalyzed cyclization of 2-halo-*N*-acylanilines,[10] (b) coupling of 2-aminophenols with carboxylic acid derivatives, which is either catalyzed by strong acids or microwave conditions,[11] (c) the oxidative cyclization of phenolic Schiff bases derived from the condensation of 2-aminophenols and aldehydes. In the latter reactions, various oxidants such as DDQ,[12] $Mn(OAc)_3$,[13] $PhI(OAc)_2$,[14] $ThClO_4$,[15] $BaMnO_4$,[16] NiO_2,[17] and $Pb(OAc)_4$[18] have been used. In addition, catalytic oxidative reactions using oxygen as an oxidant have received much attention because of their green and atom economy chemistry. The aerobic catalytic synthesis of benzoxazoles promoted by activated carbon,[19] copper nanoparticles[20] and 4-methoxy-TEMPO as an organic catalyst[21] has recently been reported. However, these reactions require the use of large amounts of the catalyst or excess base. In some of them the yields were not satisfactory. Therefore, a more effective and environmentally friendly process is needed. The synthesis of molecules with desirable functional groups in the absence of catalysts and drastic conditions continues to be of great interest. The electroorganic synthesis, through the electron-transfer-driven reactions, has been widely used,[22] while the potential applications have still not been fully utilized. Following our experience in electrochemical synthesis of organic compounds under green conditions,[23] herein we wish to describe a one-pot and straightforward protocol for the synthesis of some benzoxazole derivatives. This idea prompted us to investigate the electrochemical oxidation of 3,5-di-*tert*-butylcatechol in the presence of benzylamine derivatives. This method represents a facile and one-pot electrochemical process for the synthesis of some benzoxazole derivatives with antimicrobial activities,[24] in high yields and purities *via* electrochemical oxidation of 3,5-di-*tert*-butylcatechol in the presence of benzylamine derivatives under green conditions, without toxic reagents and solvents in a divided cell using an environmentally friendly method at a carbon electrode. This mild aqueous reaction expands the repertoire of aqueous chemistries available for small molecules.

Results and discussion

Mechanistic studies

Cyclic voltammogram of a 0.1 mM solution of 3,5-di-*tert*-butylcatechol (**1**) in a water–ethanol (70 : 30 v : v) solution containing 0.2 M phosphate buffer (pH 7.5) is shown in Fig. 1 (curve

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†Electronic supplementary information (ESI) available: FT-IR, ^{1}H NMR, ^{13}C NMR and MS spectra of compounds **6a–6e**. See DOI: 10.1039/c3gc40954f

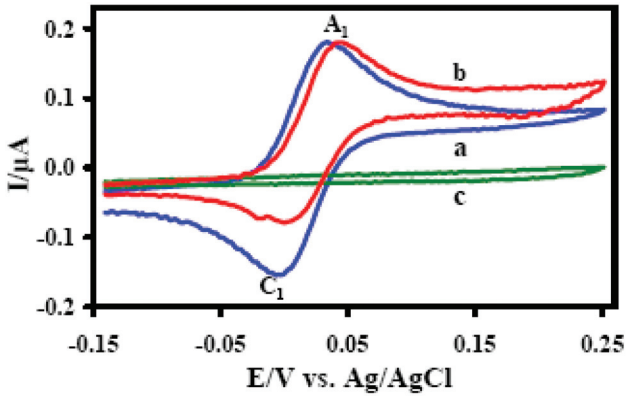


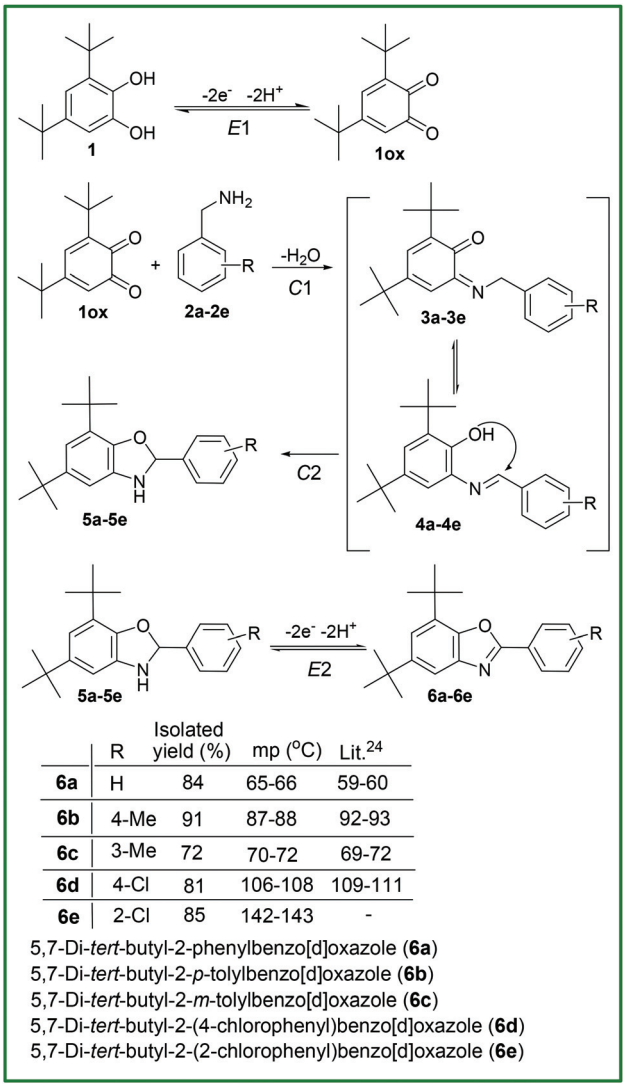
Fig. 1 Cyclic voltammograms of 0.1 mM 3,5-di-*tert*-butylcatechol (**1**): (a) in the absence, (b) in the presence of 30 mM 4-methylbenzylamine (**2b**) and (c) 30 mM **2b** in the absence of **1**, at a glassy carbon electrode, in aqueous solution containing 0.2 M phosphate buffer (c = 0.2 M, pH = 7.5). Scan rate: 2.5 mV s^{-1}; t = 25 ± 1 °C.

a). As can be seen, the anodic peak (A_1) and the corresponding cathodic peak (C_1) were obtained, which corresponds to the transformation of **1** to *o*-benzoquinone **1ox** and vice versa within a quasi-reversible two-electron process (Scheme 1).[25] Under these conditions, the peak current ratio (I_{pC1}/I_{pA1}) of nearly unity, particularly during the repetitive recycling of potential, can be considered as a criterion for the stability of *o*-benzoquinone **1ox** produced at the surface of the electrode. In other words, any side reactions are too slow to be observed on the time scale of cyclic voltammetry. The oxidation of **1** in the presence of 4-methylbenzylamine (**2b**) as a nucleophile was studied in some detail. Fig. 1 (curve b) shows the cyclic voltammogram of 3,5-di-*tert*-butylcatechol (**1**) in the presence of 4-methylbenzylamine (**2b**). As can be seen, the cathodic peak C_1 has decreased. The occurrence of a chemical reaction after the electrochemical process is supported by the decrease in the current of peak C_1 during the reverse scan, which could indicate that *o*-benzoquinone **1ox** formed at the surface of the electrode is consumed by a chemical reaction with **2b**.[25]

The current of peak C_1 strongly depends on the potential sweep rate (Fig. 2). At lower scan rates, the peak current ratio (I_{pC1}/I_{pA1}) is less than one and increases when the sweep rate increases. A similar situation was observed when the **2b** to 3,5-di-*tert*-butylcatechol (**1**) concentration ratio was decreased.

Controlled-potential coulometry was performed in a water–ethanol solution containing phosphate buffer (c = 0.1 M and pH = 7.5) and 0.25 mmol of 3,5-di-*tert*-butylcatechol (**1**) and 0.25 mmol of 4-methylbenzylamine (**2b**) at 0.2 V *versus* Ag/AgCl. The electrolysis progress was monitored using linear sweep voltammetry (Fig. 3).

As shown, the following changes are observed: (a) a decrease in the anodic peak current A_1 and (b) the appearance of the anodic peak current A_2 at slightly more positive potentials. The anodic peak A_1 disappeared when the charge consumption was 2.2 e^- per molecule of **1**. In addition, all the anodic peaks (A_1 and A_2) disappeared when the charge consumption was 4.3 e^- per molecule of **1** (Fig. 4).



	R	Isolated yield (%)	mp (°C)	Lit.[24]
6a	H	84	65-66	59-60
6b	4-Me	91	87-88	92-93
6c	3-Me	72	70-72	69-72
6d	4-Cl	81	106-108	109-111
6e	2-Cl	85	142-143	-

5,7-Di-*tert*-butyl-2-phenylbenzo[d]oxazole (**6a**)
5,7-Di-*tert*-butyl-2-*p*-tolylbenzo[d]oxazole (**6b**)
5,7-Di-*tert*-butyl-2-*m*-tolylbenzo[d]oxazole (**6c**)
5,7-Di-*tert*-butyl-2-(4-chlorophenyl)benzo[d]oxazole (**6d**)
5,7-Di-*tert*-butyl-2-(2-chlorophenyl)benzo[d]oxazole (**6e**)

Scheme 1

Diagnostic criteria of cyclic voltammetry and controlled potential coulometry accompanied by the spectroscopic data of the final products (see ESI†) indicate that the reaction mechanism of electrochemical oxidation of 3,5-di- *tert*-butylcatechol (**1**) in the presence of benzylamines **2a–2e** is *ECCE*, "electron transfer + chemical reaction (imine formation) + chemical reaction (cyclization) + electron transfer" (Scheme 1).[25] According to this Scheme, the generation of *o*-benzoquinone **1ox** is followed by a condensation reaction with benzylamine **2** at the most electrophilic carbonyl of **1ox** and generates intermediate imine **3** (*imine formation*). Intermediate **3** then is converted to the Schiff base **4**. In the next step, the Schiff base **4** *via* a cyclization reaction is converted to benzoxazoline **5**. In the final step, electrochemical oxidative dehydrogenation of benzoxazoline **5** leads to the corresponding benzoxazole **6** as the final product.

In the Schiff base **4**, the imine function may be further attacked by the excess amine to form the secondary amine

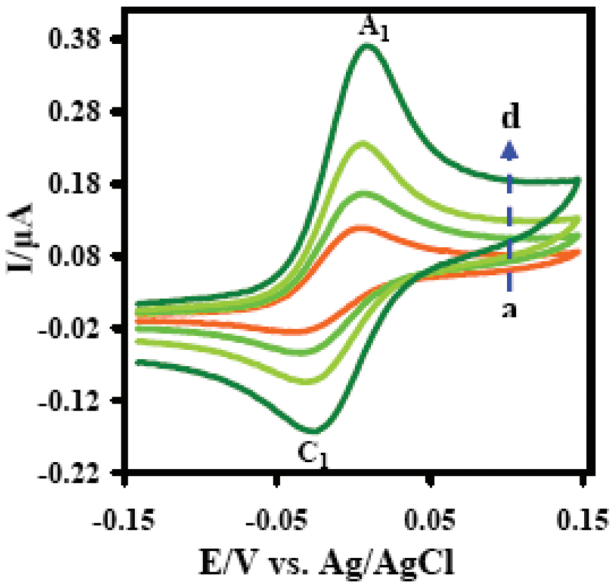


Fig. 2 Cyclic voltammograms of 0.1 mM 3,5-di-*tert*-butylcatechol (**1**) in the presence of 30 mM 4-methylbenzylamine (**2b**) at various scan rates. Scan rates from (a) to (d) are: 2.5, 5, 10 and 20 mV s^{-1}, at a glassy carbon electrode, in aqueous solution containing 0.2 M phosphate buffer pH 7.5; t = 25 ± 1 °C.

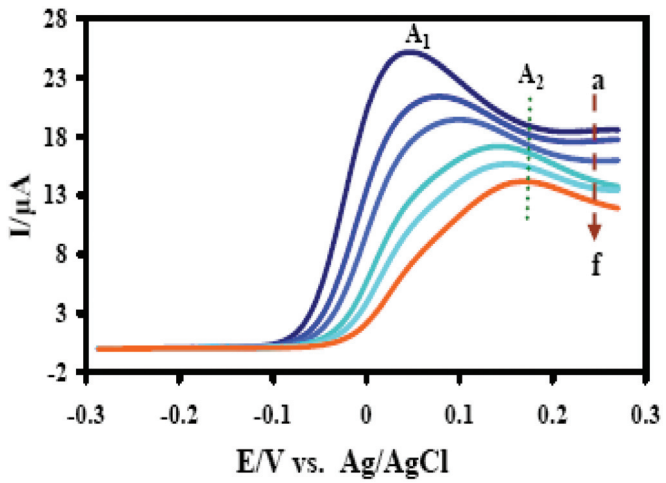


Fig. 3 Linear sweep voltammograms of 0.25 mmol 3,5-di-*tert*-butylcatechol (**1**) in the presence of 0.25 mmol 4-methylbenzylamine (**2b**) during controlled potential coulometry at 0.2 V *versus* Ag/AgCl. After consumption of: (a) 0, (b) 10, (c) 20, (d) 30, (e) 40 and (f) 50 C.

($PhCH_2NHCH_2Ph$). Largeron and Fleury used this principle for chemoselective synthesis of secondary amines.[26] But under our experimental conditions the Schiff base **4** undergoes a cyclization reaction to generate benzoxazoline **5** (Scheme 1).

Five primary benzylamine derivatives with *ortho* and *para* substituents (**2a–2e**) were used in this work for the synthesis of substituted benzoxazoles (**6a–6e**) by the *in situ* formation of the Schiff base **4** in good yields. For more data, electrochemical oxidation of 3,5-di-*tert*-butylcatechol (**1**) has also been studied in the presence of secondary benzylamines

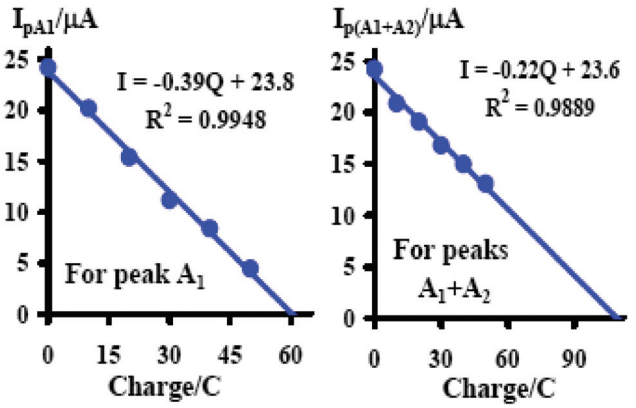


Fig. 4 Variation of peak current during controlled potential coulometry for peaks A_1 and "$A_1 + A_2$" *versus* charge consumed.

N-methyl and *N*-benzylamine. In these cases, our attempts to synthesise the benzoxazole were unsuccessful.

Galvanostatic studies

The applicability of the electrochemical synthesis of the product was improved by means of galvanostatic electrolysis. Constant-current synthesis was performed under the same conditions as described above. To take the high product yield, some affecting electrosynthesis factors must be optimized. Among the electrochemical parameters for the synthesis of organic or inorganic compounds, the current density is one of the most important factors influencing the yield and purity. This factor can also play an important role in determining the dominant reaction at the surface of the electrode. Therefore, in this work, the current density varied from 0.1 to 1 mA cm^{-2}, while the other parameters (temperature = 298 K, charge consumed = 100 C, electrode surface: 50 cm^2, 3,5-di-*tert*-butylcatechol: 0.25 mmol, and 4-methylbenzylamine (**6b**): 0.25 mmol) are kept constant. Fig. 5 shows the effect of current density on the yield of **6b**. As can be seen the highest product yield was obtained at lower current densities (0.2 mA cm^{-2}). Higher current densities result in an increase in side reactions such as the oxidation of water and secondary reactions, resulting in a decrease in product yield.

For more data on galvanostatic studies, constant-current coulometry was performed in an aqueous ethanol (70 : 30 v : v) solution containing 0.25 mmol of **1** and 0.25 mmol of **2b** in a divided cell, under a low constant current density (0.2 mA cm^{-2}). The monitoring of electrolysis progress was carried out by cyclic voltammetry. It is shown that, proportional to the advancement of coulometry, the current of anodic peak A_1 decreases. The variation of the anodic peak A_1 *versus* charge consumed is indicated in Fig. 6.

In addition, the current efficiency for various current densities was examined (Fig. 7). In this study, the current density varied from 0.25 to 5 mA cm^{-2}, while the other parameters (temperature = 298 K, charge consumed = 100 C, electrode surface: 50 cm^2, 3,5-di-*tert*-butylcatechol: 0.25 mmol, and 4-methylbenzylamine, **6b**: 0.25 mmol) are kept constant. The

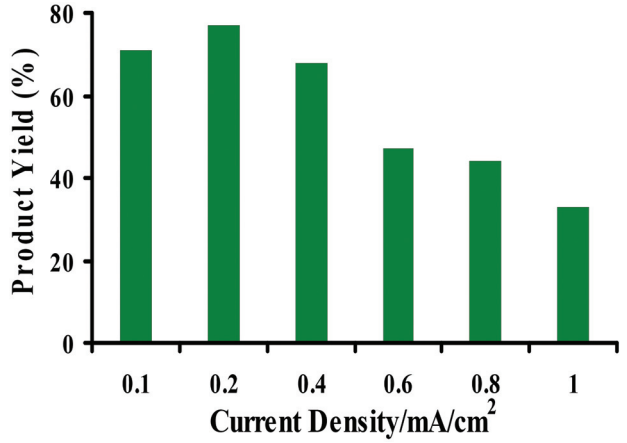


Fig. 5 Effect of current density on the yield of **6b**. Charge passed: 1 F mol^{-1}. Charge consumed = 100 C. Electrode surface: 50 cm^2.

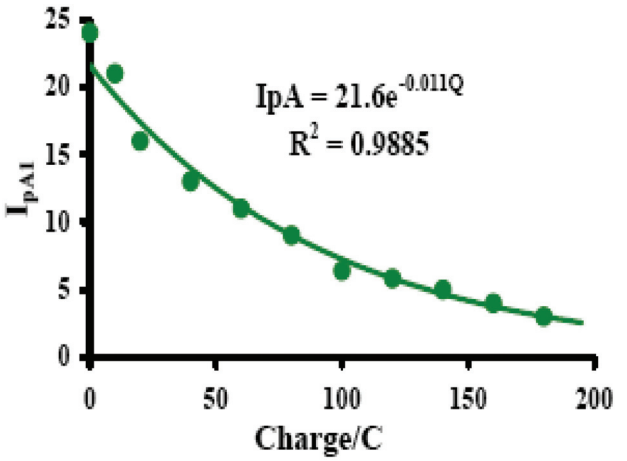


Fig. 6 Variation of I_{pA1} *vs.* charge consumed during constant current coulometry of 3,5-di-*tert*-butylcatechol (**1**) (0.25 mmol) in the presence of 0.25 mmol 4-methylbenzylamine (**2b**). Current density: 0.2 mA cm^{-2}. Electrode surface: 50 cm^2.

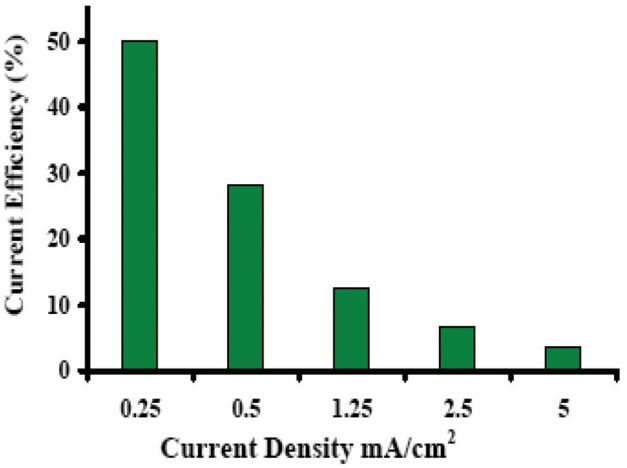


Fig. 7 Effect of current density on the current efficiency of synthesis of **6b**. Charge passed: 1 F mol^{-1}. Charge consumed = 100 C. Electrode surface: 50 cm^2.

results show that, with increasing the current density the current efficiency decreases. Increasing the current density increases the side reactions such as oxidation of water or other secondary reactions, resulting in a decrease in current efficiency.

Conclusions

The present method for the synthesis of 2-arylbenzoxazoles has several advantages over conventional methods. (a) This process is practically convenient to carry out and can be performed at atmospheric pressure. (b) Neither catalyst nor organic/inorganic oxidizing agents are necessary and the reaction can be performed under green and mild condition. (c) The *in situ* formation of Schiff bases is achieved and there is no need to prepare Schiff bases in advance.[15] In summary, we have reported an efficient method for the preparation of benzoxazole containing molecules using a one-pot electrochemical process. The extension of this electrochemical system for the preparation of other useful heterocycles is under way in our laboratory. To the best of our knowledge, this is the first example in which benzoxazoles have been obtained directly and efficiently from the electrooxidation of 3,5-di-*tert*-butylcatechol in the presence of benzylamines using water as a reaction medium in the absence of any catalyst and/or oxidant. Finally, although the experiments were conducted on a relatively small scale, there is little difficulty in producing larger quantities either by using larger cells or by running several cells in series.

Experimental section

General remarks

Reaction equipment is described in an earlier paper.[27] 3,5-di-*tert*-butylcatechol and benzylamine derivatives were purchased from Aldrich. These chemicals were used without further purification. The purity of products has been checked by TLC, and characterization has been done using ^{1}H NMR, ^{13}C NMR, IR spectroscopic techniques and mass spectrometry.

Electroorganic synthesis of 6a–6e

Controlled-potential method. A mixture (70 mL) of water (phosphate buffer, c = 0.1 M, pH = 7.5)–ethanol (70/30 v/v) containing 0.25 mmol of 3,5-di-*tert*-butylcatechol and 0.25 mmol of benzylamine derivative was subjected to electrolysis at 0.20 V *versus* Ag/AgCl in a divided cell. The electrolysis was terminated when the decay of current became more than 95%. The precipitated solid was collected by filtration and was washed several times with water. The crude product is then recrystallized in methanol (or *n*-hexane). In the case of **6c**, thin layer chromatography (acetone–*n*-hexane 1 : 8) was used for separation of the product. After drying, the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS. In this work, ethanol

was used as a co-solvent for the solubility of 3,5-di-*tert*-butylcatechol in the electrolysis medium.

Galvanostatic method. A mixture (70 mL) of water (phosphate buffer, c = 0.1 M, pH = 7.5)–ethanol (70/30 v/v) containing 0.25 mmol of 3,5-di-*tert*-butylcatechol and 0.25 mmol of benzylamine derivative was electrolyzed in a divided cell equipped with a carbon anode (an assembly of four rods, with 50 cm^2) and a large platinum gauze cathode at 25 °C under a constant-current density of 0.2 mA cm^{-2}. The quantity of the electricity passed was determined using the exponential curve and the related equation in Fig. 6. The other steps are similar to those described above in the controlled-potential method. The IR, ^1H and ^{13}C NMR, and mass spectra of compounds **6a–6d** are identical to those reported by Vinsova *et al*[24] (for the data, see ESI†). The yields and melting points of compounds **6a–6e** are shown in Scheme 1.

5,7-Di-*tert*-butyl-2-(2-chlorophenyl)benzo[*d*]oxazole (6e). IR (KBr, cm^{-1}): 2957, 2907, 2867, 1598, 1572, 1554, 1481, 1463, 1438, 1400, 1366, 1331, 1306, 1265, 1085, 1043, 1008, 934, 838, 818, 735, 768, 735. ^1H NMR (90 MHz, $CDCl_3$): ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H, CH_3), 1.56 (s, 9H, CH_3), 7.36 (d, 1H, Ar), 7.44 (m, 2H, Ar), 7.57 (m, 1H, Ar), 7.73 (d, 1H, Ar), 8.18 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.3, 32.1, 34.7, 35.4, 114.8, 120.2, 127.0, 127.2, 131.7, 131.9, 132.1, 133.6, 142.1, 147.3, 148.2, 160.9. MS (EI) m/z (relative intensity): 341.1 (35), 326.1 (100), 270 (10).

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