DOI: 10.1002/adsc.200800317

Reusable Cobalt(III)-Salen Complex Supported on Activated Carbon as an Efficient Heterogeneous Catalyst for Synthesis of 2-Arylbenzimidazole Derivatives

Hashem Sharghi,[a,*] Mahdi Aberi,[a] and Mohammad Mahdi Doroodmand[a]

[a] Department of Chemistry, Shiraz University, Shiraz, 71454, I. R. Iran
Fax: (+98)-711-228-0926; phone: (+98)-711-228-4822; e-mail: shashem@chem.susc.ac.ir or hashemsharghi@gmail.com

Received: May 21, 2008; Revised: July 29, 2008; Published online: October 7, 2008

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800317.

Abstract: Various 2-arylbenzimidazoles were synthesized from phenylenediamines and aromatic aldehydes *via* a one-step process in the presence of a catalytic amount of a cobalt-salen complex supported on activated carbon [CoxO-Co(salen) **11**] at room temperature. The salient features of this method include mild conditions, short reaction times, high yields, easy purification, recyclable catalyst, large-scale synthesis and simple procedure. The reactions were performed in ethanol and the catalyst could be reused for several cycles without a decrease in activity. The heterogeneous catalyst was characterized by powder X-ray diffraction (XRD), scanning electron microscopy (SEM), atomic forced microscopy (AFM), thermogravimetric (TG) methods for analysis of nitrogen adsorption and FT-IR spectroscopy. Leaching experiments showed that the catalyst is most strongly anchored to the activated support after 10 cycles of reuse.

Keywords: activated carbon; 2-arylbenzimidazoles; cobalt-salen complexes; recyclable catalyst

Introduction

The benzimidazole ring is an important pharmacophore in modern drug design and discovery.[1] Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcer agents, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics to name just a few.[2–4,5a] In addition, benzimidazoles are very important intermediates in organic reactions.[1b,6] The extensive interest in benzimidazole-containing structures has prompted widespread studies for their synthesis. There are two general methods for the synthesis of 2-substituted benzimidazoles. The first is the coupling of phenylenediamines and carboxylic acids[7] or their derivatives (nitriles, imidates, or orthoesters),[8] which often requires strong acidic conditions, and sometimes combined with very high temperatures (i.e., PPA, 180 °C) or the use of microwave irradiation.[9] The second route involves a two-step procedure that includes the oxidative cyclodehydrogenation of aniline Schiff's bases, which are often generated *in situ* from the condensation of phenylenediamines with aldehydes.[5] Various oxidative reagents such as nitrobenzene (high-boiling point oxidant/solvent),[10] 1,4-benzoquinone,[11] air,[5] $In(OTf)_3$,[1b] $PhI(OAc)_2$,[12] Zn-proline,[13] heteropoly acids,[14] thionyl chloride-treatment,[15] DDQ,[16] electron-deficient olefins,[17] benzofuroxan,[18] MnO_2,[19] $Pb(OAc)_4$,[20] oxone,[21] $NaHSO_3$,[22] H_2O_2/HCl[23] and $Na_2S_2O_5$[24] have been employed. Because of the availability of a vast number of aldehydes, the condensation of phenylenediamines with aldehydes has been extensively used. However, many of these methods have some drawbacks such as low yields, long reaction times, drastic reaction conditions, tedious work-up procedures, co-occurrence of several side reactions and in some cases more than one step is involved in the synthesis of these compounds. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Therefore, the search continues for a better catalyst for the synthesis of benzimidazoles in terms of operational simplicity, reusability, economic viability, and greater selectivity.

Activated carbons are porous, readily available, and have high thermal and chemical stabilities and very low cost. Besides the advantages mentioned above, active carbons are among the materials that have the largest specific surface area, easily reaching values of

$>1000\ m^2\ g^{-1}$. Because of their high surface area and high porosity, active carbons have been used as supports for many noble metal-based heterogeneous catalysts, particularly palladium on charcoal. The structure of active carbons, although not periodic and uniform, is being increasingly understood, and the presence of functional groups able to intervene in covalent anchoring, particularly carboxyl and hydroxy groups, is recognized. The population of surface hydroxy groups can be maximized by chemical oxidation and mild partial combustion processes.[25]

The activated carbons and single-wall carbon nanotubes (SWNTs), have been used for the immobilization of chiral salen-metal complexes and have attracted much recent interest.[25,26]

Herein we report a simple and highly selective procedure for the condensation reaction of *o*-phenylenediamine derivatives with different aldehydes using metal-salen complexes in homogeneous and heterogeneous types whereby molecular oxygen is utilized as the sole green oxidant without any additives in ethanol at ambient temperature.

Results and Discussion

Using Metal-Salen Complexes for the Synthesis of Benzimidazole Derivatives

Metal-salen complexes have been recognized as being among the most promising catalysts for various reactions. These complexes show wide applicability, and are now used as catalysts for a variety of enantioselective reactions, such as oxidation,[27,28] the Diels–Alder reaction,[29] the addition of TMSCN to aldehydes,[30] and the conversion of 1,2-epoxyethanes to 2-haloethanols with molecular halogen.[31]

In conjunction with ongoing work in our laboratory on the synthesis and formation of metal-salen complexes with different molecules,[31,32] we found that these complexes efficiently catalyzed the condensation reaction of *o*-phenylenediamine derivatives with different aldehydes to form benzimidazoles in ethanol (Scheme 1).

In this study, the preparation of benzimidazoles from *o*-phenylenediamines and aryl aldehydes in the presence of a catalytic amount of cobalt-salen complex was examined.

In a general procedure, to a mixture of *o*-phenylenediamine and benzaldehyde in ethanol, was added a solution of the catalyst in ethanol and the mixture was stirred at room temperature. With regard to the amount of *o*-phenylenediamine, 5 mol% of catalyst was used.

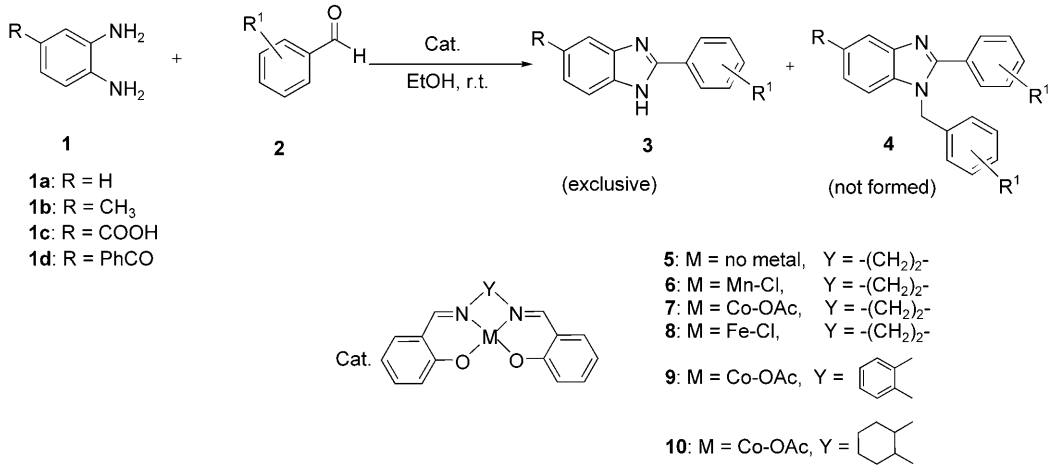
While the condensation reaction of *o*-phenylenediamine with benzaldehyde in the absence of the catalyst (Table 1, entry 1) or absence of the metal in the salen structure (Table 1, entry 2) led to a very little product, metal-incorporated salen structures, showed auspicious results as shown in Table 1 (entries 3–7).

Furthermore, three different metallic ions were tested. The reaction times and yields of 2-phenylbenzimidazole in the presence of various metal(III)-salen

Table 1. The condensation reaction of *o*-phenylendiamine (1.0 mmol) with benzaldehyde (1.0 mmol) using different metal(III)-salen complexes (5 mol%) in ethanol at room temperature.

Entry	Catalyst	Time [h]	Yield[a] [%]
1	–	12	<10
2	**5**	12	<10
3	**6**	5	58
4	**7**	0.5	90
5	**8**	0.5	74
6	**9**	0.5	87
7	**10**	0.5	96

[a] Isolated yield.



Scheme 1.

complexes (Mn, Co, Fe) are summarized in Table 1 (entries 3–5). Among the metal-incorporated catalysts examined, the use of Co(III)-salen **7** gave the best results in terms of yield and reaction rate.

In the next step in order to examine the effect(s) of ligands on the catalysis of the reaction, three different kind of ligands were employed (Table 1, entries 4, 6 and 7).

It was of great importance that the reaction was largely affected by the various ligands of the complexes. Among the three different ligands tested, the use of catalyst Co(salen) **10** was found to be the most effective and the reaction was completed within 30 min with the best outcome (Table 1, entry 7). In the presence of other catalysts the reaction times and yields were of lower quality as shown in the Table 1 (entries 4, 6 and 7).

According to Table 2, the best results were obtained with the use of 5 mol% of cobalt-salen **10**. When the amount of the catalyst was reduced, the yield of the products decreased, whereas raising the catalyst concentration did not lead to an appreciable increase of the yield and a shorter reaction time.

The effect of solvents on the condensation reaction utilizing cobalt-salen complex **10** was also investigated as shown in Table 3. We found that these reactions appeared to be largely dependent on the nature of the solvent. Obviously, ethanol stands out as the solvent of choice with its fast reaction rate, high yield, selectivity, cheapness and environmental acceptability.

Only a little benzimidazole would be obtained if this reaction was operated in a nitrogen atmosphere (Table 3, entry 9). That is to say, O_2 played an important role in this reaction. Using the obtained optimized conditions, to investigate the oxygen effect, instead of a static atmosphere of air, a continuous flow of O_2 was bubbled through the reaction mixture, but the rate was not accelerated showing that O_2 dissolved in the solvent and absorbed by surface adsorbtion is sufficient for an efficient reaction process.

Table 2. The optimal cobalt-salen percentage amount (mol%) towards the 2-phenylbenzimidazole synthesis.

Entry	Mol% of catalyst	Time [min]	Yield[a] [%]
1	1	30	28
2	3	30	51
3	5	30	96
4	10	30	96
5	20	30	96

[a] Isolated yield.

Table 3. Effect of different solvents in the condensation reaction of *o*-phenylenediamine (1.0 mmol) with benzaldehyde (1.0 mmol) at room temperature using Co(III)-salen **10** (5 mol%).

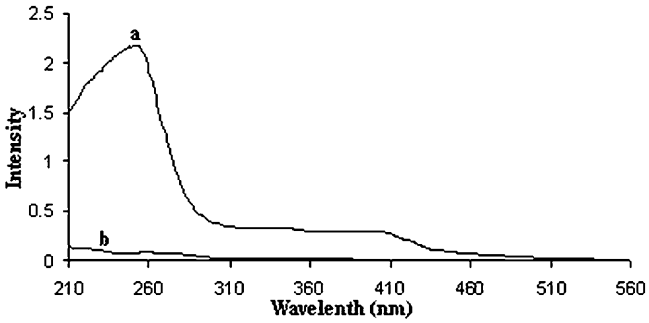
Entry	Solvent	Time [min]	Yield of product **3**[a] [%]	Yield of by-product **4**[a] [%]
1	MeOH	30	92	5
2	EtOH	30	96	0
3	MeCN	120	42	6
4	Dioxane	120	30	12
5	THF	120	35	14
6	DMF	180	<10	0
7	CH_2Cl_2	180	<10	1
8	H_2O	60	46	8
9	EtOH	240	30[b]	0

[a] Isolated yield.
[b] Operated under a nitrogen atmosphere.

Preparation of the Heterogeneous Supported Catalysts

Since the Co(III)-salen **10** proved to be the best catalyst among the cobalt-salens for benzimidazole synthesis, we set forth to prepare a new heterogeneous catalyst by a simple impregnation of Co(III)-salen **10** onto activated carbon. An air-oxidized activated carbon (Cox)[33] was refluxed with an aqueous solution of sodium hydroxide to form CoxONa. In the next step, 1.00 g of the resulting CoxONa was allowed to reflux with a solution of Co(III) salen **10** [0.10 g of Co(salen) **10** in 10 mL EtOH] under N_2 in 20 mL of absolute EtOH for 1 h. The anchoring process was followed by UV-Vis spectroscopy (Scheme 2). The resulting supported complexes were then separated, dried and their cobalt content was examined by an inductively coupled plasma (ICP) analyzer. To evaluate the cobalt content, the supported catalyst was treated with concentrated HCl (5.0 M) and HNO_3 (5.0 M), followed by ICP analysis. The cobalt content was determined to be 8.94% w/w, which is close to the expected value of 9.04% w/w.

The new successful heterogeneous cobalt-salen catalyst synthesized by this simple anchoring procedure, was characterized by some electron microscopic and



Scheme 2. Monitoring the supporting process of cobalt salen by the UV-Vis, (**a**): before and (**b**): after being supported on activated carbon.

spectroscopic techniques such as SEM, AFM, and XRD. The thermal stability of the cobalt-salen complex coated on activated carbon was also analyzed using a self-made TG instrumentation system.[34] The nitrogen adsorption of the cobalt-salen complex on activated carbon validated that that the cobalt-salen complex was well coated on the activated carbon. This technique was achieved *via* the flowing of a trace amount of nitrogen gas through the sample and following the changes in the weight percentage of cobalt supported on activated carbon using TG analysis.

Before supporting the cobalt-salen complex on the carbon substrate, the carbon powders were activated *via* flowing a trace amount of oxygen[35] through carbon powders located in a quartz tube inside a furnace at 200 °C for about 2 h. The operating conditions for the activation and functionalization processes were optimized based on FT-IR spectrometry. Activation of carbon powders resulted to the formation of hydroxy groups. Further oxidation of carbon powder causes oxidation of hydroxy groups to carboxylic functional groups. The FT-IR spectra of carbon powders reveal the formation of carboxylic acid groups. The sharp peak at around 3448 cm^{-1} is correlated with the hydroxy bond (O–H) formed during the activation process.[36] Electron microscopy such as SEM is a precise instrumentation method for the direct observation of non-material samples.[37] AFM is also used to study the topography of the elements at micro and nano scales.[38] In this research, samples of the cobalt-salen complex suspended on activated carbon as substrate were observed using SEM and AFM. The SEM (Figure 1) and AFM images (Figure 2, **a**: 2-D and Figure 2, **b**: 3-D), show that the cobalt nanoparticles with different sizes have been dispersed on the activated carbon substrate. According to the images of electron microscopy, the average size of the cobalt particles on the carbon substrate is estimated to be around 120 nm. Based on the voltage profile of the AFM image (Figure 2, **c**), the width of the band at half height of the voltage profile peak reveals the size of cobalt nanoparticles. This has been estimated at about 112 nm. The histogram (Figure 3) shows a distribution of cobalt nanoparticles between 50 to 500 nm. The XRD patterns of both activated carbon and cobalt nanoparticles supported on carbon (Figure 4) reveal a single phase of cobalt nanoparticle structure along with the amorphous nature of activated carbon as substrate. As shown in Figure 4, the strongest peaks of the XRD patterns correspond to the planes of activated carbon whereas other peaks at $\theta = 22.5°$ and 25.0° are related to the supported cobalt particles.[39] The same results were also obtained for the XRD patterns of the cobalt-salen complex after its use as catalyst in the synthetic organic reaction for at least 10 cycles. This reveals the excellent stability and recovery of the doped cobalt-salen complex on activated carbon.

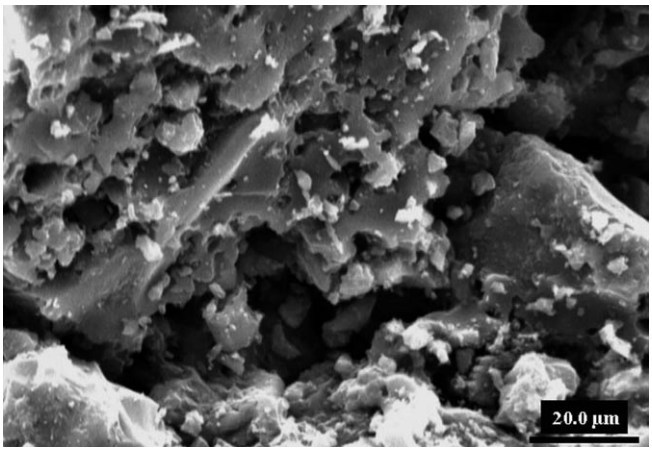


Figure 1. SEM image of the cobalt-salen complex coated on activated carbon.

ICP results showed 98.3% recovery for this anchoring procedure. In order to validate the result of ICP analysis, the thermal stability of cobalt nanoparticles on activated carbon was also investigated using a slefmade TG analysis instrument. Figure 5 shows the thermogram of the sample at an air flow of 3 $mL\,min^{-1}$ and temperature ramp of 2 °C min^{-1}. According to the thermogram, the weight lost at around 95 °C is related to the desorption of water vapour and other volatile organic compounds that have been adsorbed on the catalyst. Following the thermogram, the decrease observed in the slope of the diagram starting at around 130 °C is related to the oxidation of cobalt nanoparticles. At this step a slow reduction in the weight percent of Co-salen/C is observed. Also, the weight lost at around 295 °C is due to the oxidation of activated carbon. Finally, about 4.10% remaining weight percentage at the end of TG analysis reveals the amount of cobalt oxide (Co_2O_3).[40] This value shows 99.76% recovery for doping of the cobalt-salen complex on activated carbon. The small difference (~1.46%) between the results of TGA and ICP is related to the incomplete sample preparation during treatment with nitric acid prior to analysis with ICP.

The adsorption behaviours of nitrogen gas on each deactivated and activated carbon and also salen-cobalt complex supported on activated carbon have also been studied using the TG analysis instrumentation system and a nitrogen atmosphere (Figure 6). The results show that activation of carbon and also its supporting with the cobalt-salen complex cause reductions of surface activity for nitrogen adsorption of about $0.017 \pm 0.0012\%$ and $0.025 \pm 0.001\%$ wt, respectively. Therefore when carbon is activated and supported with cobalt salen complex, it is estimated to have about 0.136 $cm^3\,g^{-1}$ and 0.200 $cm^3\,g^{-1}$ reductions in nitrogen adsorption.

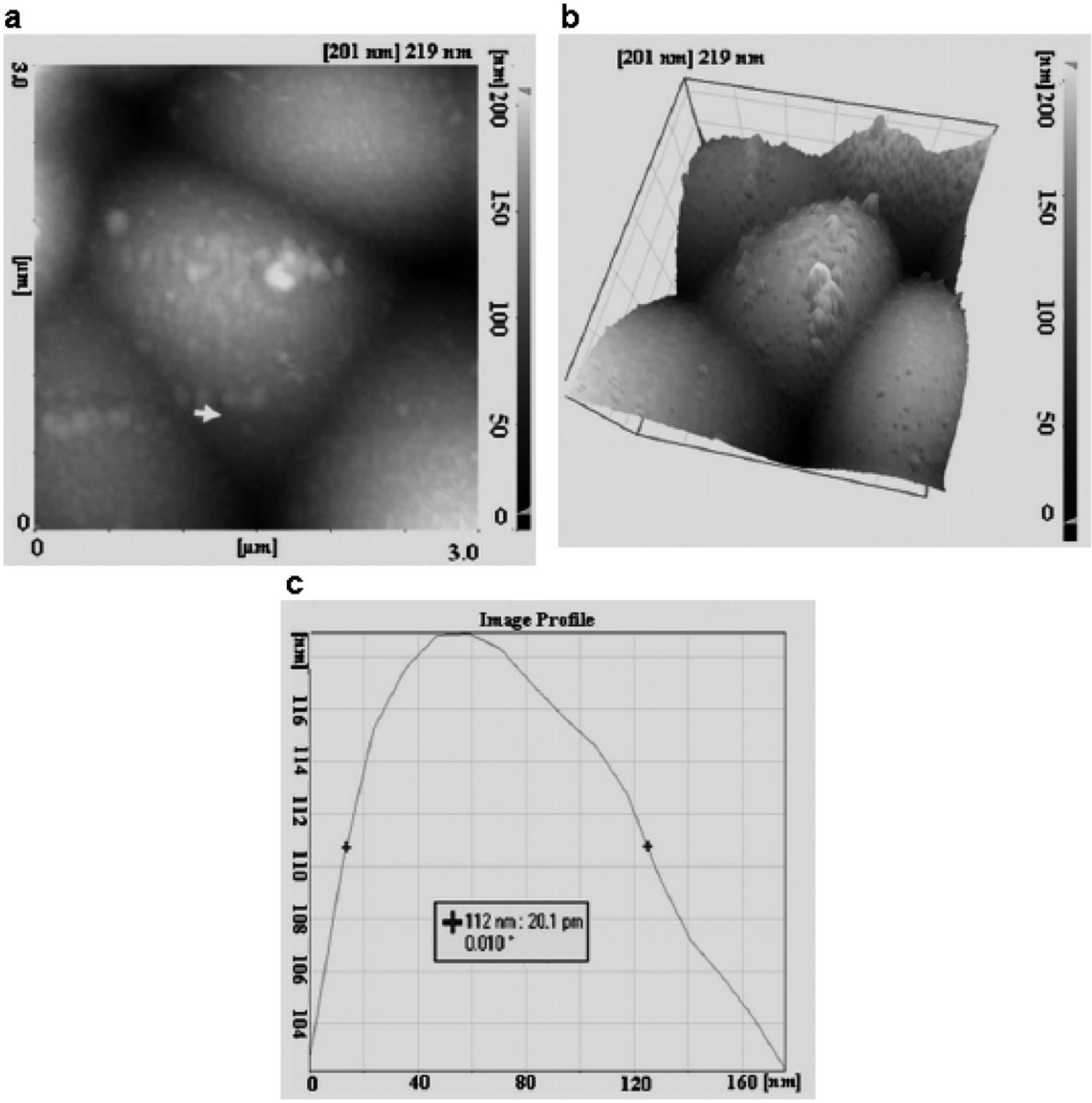


Figure 2. AFM images of the cobalt-salen complex coated on activated carbon, **a**: 2-D image, **b**: 3-D image, **c**: voltage profile.

A plausible anchoring mechanism for the cobalt-salen catalyst onto the modified air-oxidized activated carbon(Cox), considering the fact that the salen with no metallic ion could not anchor onto the activated carbon, is proposed that may involve the grafting of cobalt-salen onto activated carbon by the reaction of Co(salen) with the surface CoxONa groups to form Co–O–Cox linkages (Scheme 3). The need for a treatment with concentrated HCl to release the Co(salen) complex from activated carbon support would corroborate the proposed mechanism.

Homogeneous and Heterogeneous Catalytic Benzimidazole Synthesis

Finally, using the optimized conditions, the reaction of *o*-phenylenediamines (1 mmol) and aryl aldehydes (1 mmol) were carried out in the presence of homogeneous and heterogeneous catalysts at room temperature to give the corresponding 2-aryl-substituted benzimidazoles in high yields. Under optimized reaction conditions, we obtained exclusively 2-substituted products **3** and no *N*-alkylated products **4** were observed (Scheme 1). We studied the scope of the reaction by

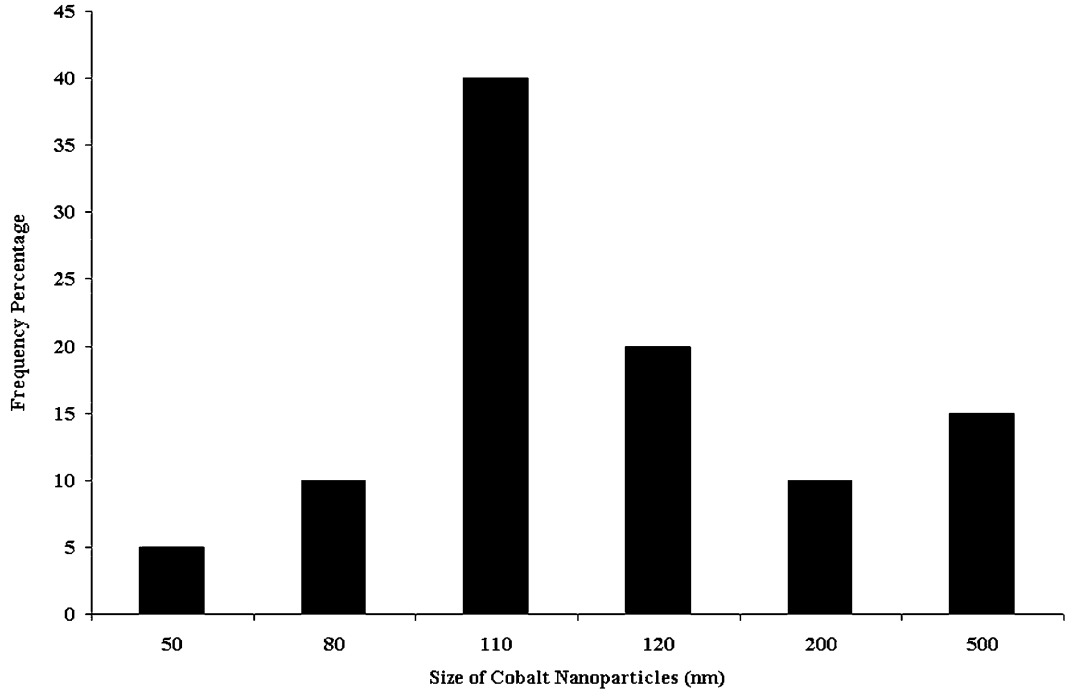


Figure 3. Histogram representing the size distribution of the cobalt-salen complex supported on activated carbon.

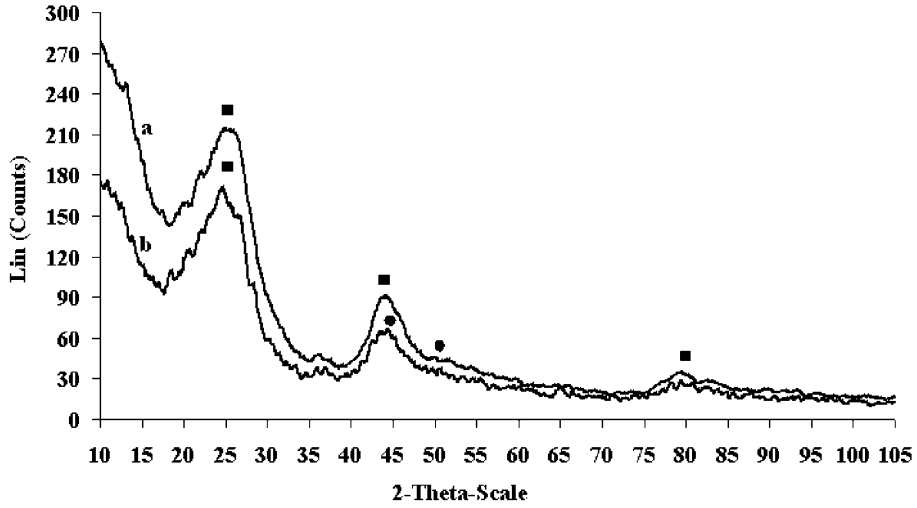


Figure 4. XRD patterns of activated carbon (**a**) and the cobalt-salen complex coated on activated carbon (**b**), amorphous carbon (■), Co (●).

varying the *o*-phenylenediamines (**1a–1d**) for condensation with benzaldehyde under the optimized conditions and the results are shown in Table 4. In the next step, we studied the generality and selectivity of the catalyst for the condensation of electronically divergent aromatic aldehydes with *o*-phenylenediamine. In all cases, the reaction was clean and carried out within 25 min to 7 h. All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. As shown, both aldehydes bearing electron-donating and electron-withdrawing substituents afforded the desired benzimidazoles in excellent yields (Table 4). Heteroaryl aldehydes, such as, 2-thiophenyl- and 2-pyridinylcarboxaldehydes (Table 4, entries 16 and 17), were also well tolerated under these mild conditions. The presented method has the ability to tolerate other functional groups such as hydroxy, methoxy, halo, nitro, and nitrile on the aryl aldehyde (Table 4, entries 5–15). As shown in Table 4 (entries 18 and 19) aliphatic aldehydes and vinylic aldehydes are not applicable for the synthesis of 2-alkylbenzimidazole derivatives in the presented procedure.

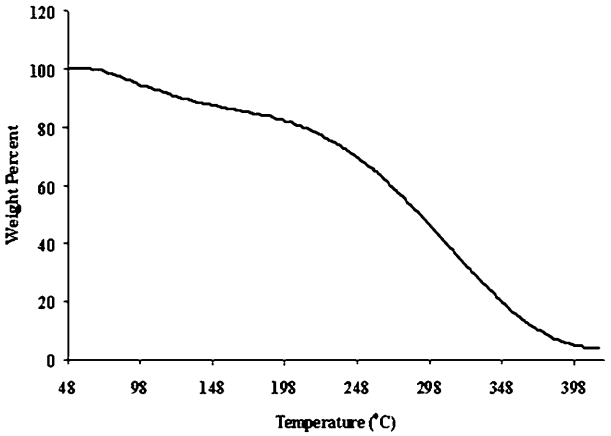


Figure 5. Thermogram of the cobalt-salen complex supported on activated carbon.

The reactivity of the heterogeneous catalyst in comparison with the homogeneous catalyst is partially increased but the selectivity of products **3** and **4** remains unchanged (Table 4).

To access the feasibility of applying this method on a preparative scale, we carried out the coupling of *o*-phenylenediamine with benzaldehyde in a 50-mmol scale in the presence of the hetereogenous catalyst. As expected, the reaction proceeded smoothly, similar to the case in a smaller scale (Table 4, entry 1), and the desired 2-phenylbenzimidazole was obtained in 96% isolated yield in 25 min. The continuous bubbling of O_2 through the reaction mixture instead of a static atmosphere of air, did not accelerate the reaction rate, as was mentioned for the smaller scale reaction.

Supporting the cobalt salen complex on activated carbon provided the chance of recovery of catalyst for the successive uses. The catalyst could be readily removed from the reaction mixture by a simple filtration and be used repeatedly for several times without appreciable loss in activity. In a typical run, *o*-phenylenediamine (1 mmol), benzaldehyde (1 mmol) and CoxO-Co(salen) **11** (0.24 g, 5 mol%) were allowed to react in ethanol at room temperature for 25 min. Then the reaction mixture was directly passed through celite and rinsed with ethanol (3×15 mL).

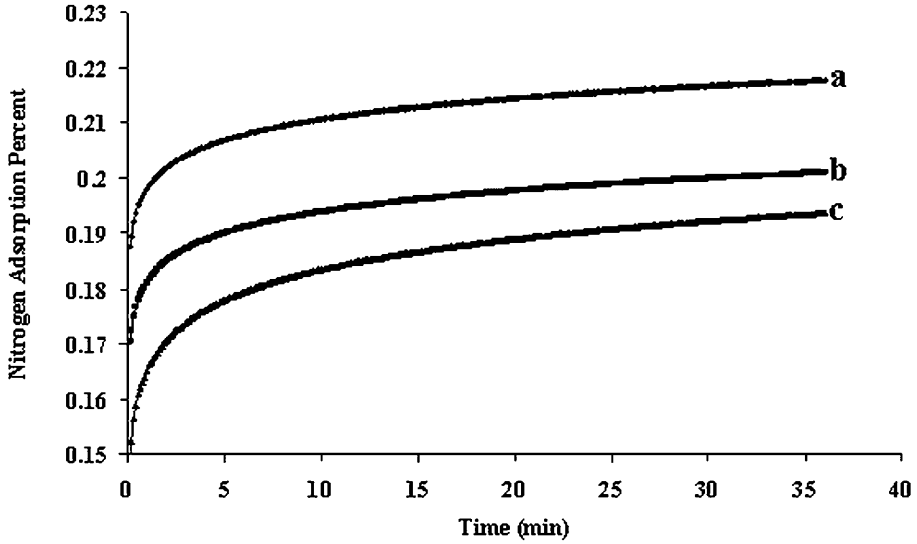
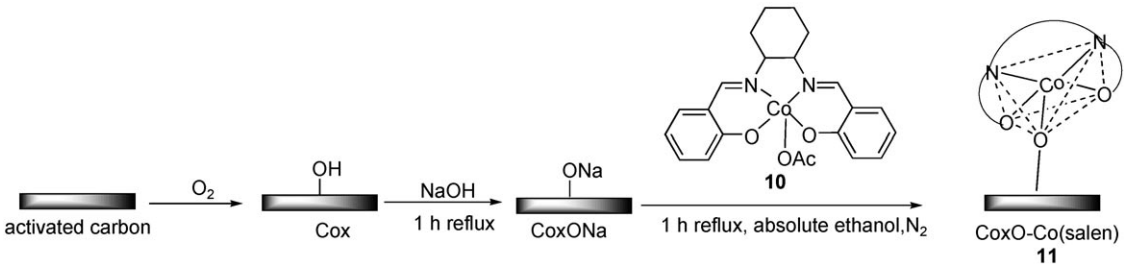


Figure 6. Comparison between the adsorption behaviour of nitrogen gas on carbon powder (**a**), carbon powder activated with oxygen (**b**) and activated carbon after deposition of the cobalt-salen complex (**c**).



Scheme 3. The proposed anchoring procedure for the Co(salen) catalyst onto a modified air-oxidized activated carbon.

Table 4. Condensation reaction of *o*-phenylenediamine (1.0 mmol) with different aldehydes (1.0 mmol) using Co(III)-salen complex **10** and CoxO-Co(salen) **11** (5 mol%) in ethanol at room temperature.

Entry	Aldehyde	*o*-Phenylenediamine	Compound **3**	Co(salen) complex **10**		CoxO-Co(salen) **11**	
				Time [min]	Yield[a] [%]	Time [min]	Yield[a] [%]
1	C_6H_5CHO	**1a**	**3a**	30	96	25	96
2	C_6H_5CHO	**1b**	**3b**	15	96	12	95
3	C_6H_5CHO	**1c**	**3c**	150	93	135	94
4	C_6H_5CHO	**1d**	**3d**	6 h	88	5.5 h	90
5	4-ClC_6H_4CHO	**1a**	**3e**	60	90	50	92
6	3-ClC_6H_4CHO	**1a**	**3f**	90	91	75	90
7	2-ClC_6H_4CHO	**1a**	**3g**	45	94	40	95
8	4-MeC_6H_4CHO	**1a**	**3h**	40	95	30	94
9	4-$MeOC_6H_4CHO$	**1a**	**3i**	45	92	40	95
10	4-CNC_6H_4CHO	**1a**	**3j**	180	85	165	90
11	4-*i*-PrC_6H_4CHO	**1a**	**3k**	40	95	30	96
12	2-HOC_6H_4CHO	**1a**	**3l**	120	90	110	92
13	4-HOC_6H_4CHO	**1a**	**3m**	90	92	80	92
14	4-$NO_2C_6H_4CHO$	**1a**	**3n**	240	90	225	92
15	3-$NO_2C_6H_4CHO$	**1a**	**3o**	150	94	135	95
16	2-thiophenyl	**1a**	**3p**	210	89	195	91
17	2-pyridinylcarboxaldehyde	**1a**	**3q**	7 h	90	6.5 h	90
18	$CH_3(CH_2)_3CHO$	**1a**	–	–	no reaction	–	no reaction
19	$CH_3CHCHCHO$	**1a**	–	–	no reaction	–	no reaction

[a] Isolated yield.

The recovered CoxO-Co(salen) **11** was dried and used for another successive reaction run and the combined filtrates were collected for product identification and quantitation. As shown in Table 5, the catalytic activity of CoxO-Co(salen) **11** remained largely unchanged even after ten consecutive runs. The ICP analysis of the recycled catalyst (after the tenth reaction run) revealed the Co content to be 8.64% w/w, which is comparable to the initial value of 8.94% w/w. As shown in Table 5, the catalytic activity of the cobalt-salen complex supported on activated carbon remained largely unchanged for ten successive runs, with a total of 191.6 turnovers being achieved.

Table 5. Catalyst recyclability studies in ethanol at room temperature.

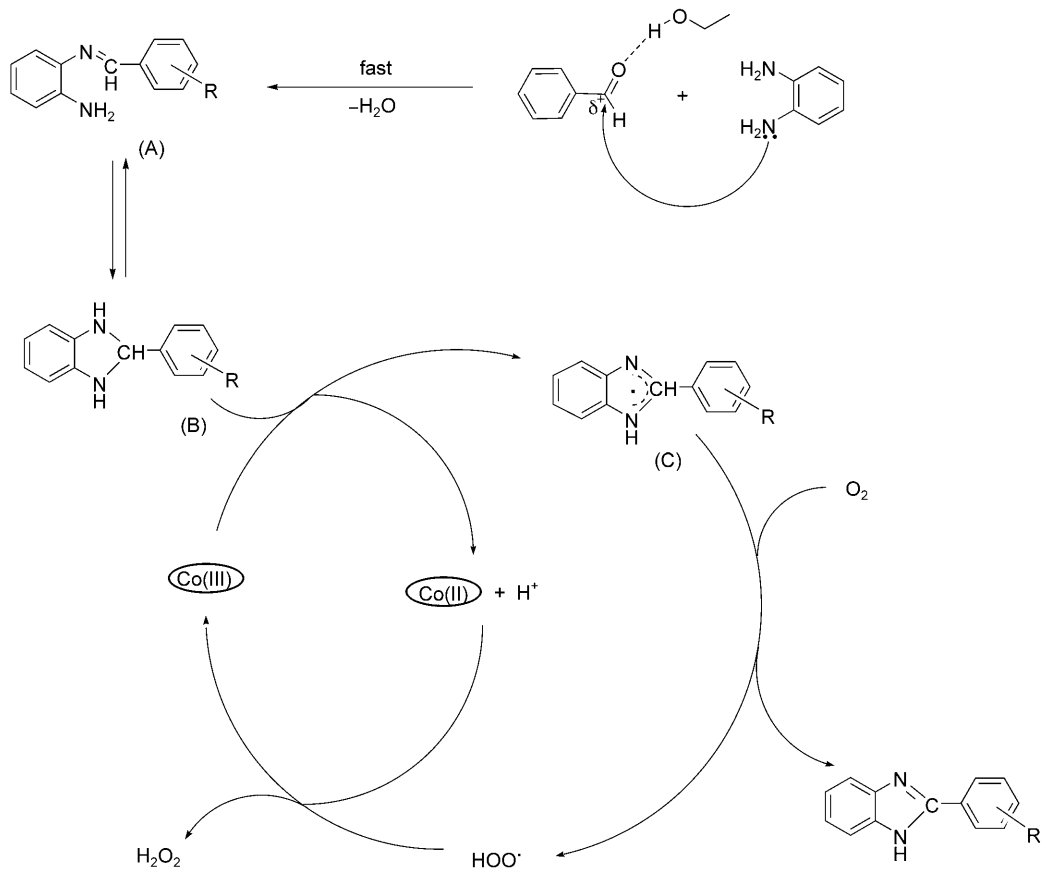
Reaction run	Time [min]	Yield [%][a]
1	25	96
2	25	96
3	25	96
4	25	96
5	25	96
6	25	96
7	25	96
8	25	96
9	25	95
10	25	95

[a] Isolated yield.

Mechanistically, we believe that the formation of benzimidazoles under these conditions follows through the known[5,9,10 16–22,24,41] intermediate Schiff's bases **A**, which exist in equilibrium with the cyclic hydrobenzimidazoles **B** that were oxidized to benzimidazoles by oxygen of the air (Scheme 4). We propose that the reaction of cyclic hydrobenzimidazoles **B** with cobalt(III)-salen proceeded by the reduction of Co(III) to Co(II), the utilization of O_2, and the concomitant generation of H_2O_2 similar to the reported experiment for the oxidation of hydroquinone by a copper(II) complex.[42] Then the oxidative dehydrogenation of adduct **C** in the presence of O_2 affords the desired 2-arylbenzimidazoles.

Conclusions

In summary, we have developed a general and efficient one-pot synthetic route to 2-arylbenzimidazoles from phenylenediamines and aromatic aldehydes using a cobalt(III)-salen complex supported on activated carbon and air (O_2) as catalyst. The mild reaction conditions, the fast reaction times, large-scale synthesis, easy and quick isolation of products, recyclable catalyst and excellent yields are the main advantages of this procedure which make it an attractive and useful contribution to the present methodologies. Hence, we believe that it will find wide application in organic synthesis as well as in industry.



Scheme 4. The proposed mechanism for the cobalt-salen complex-catalyzed reaction for the synthesis of 2-substituted benzimidazole derivatives.

Experimental Section

General Procedure for the Synthesis of 2-Substituted Benzimidazoles in the Presence of a Catalytic Amount of Co(salen) Complex 10

For each reaction, a mixture of *o*-phenylenediamine **1** (1 mmol) and aldehyde **2** (1 mmol) was stirred in 5.0 mL of EtOH in the presence of catalyst (5 mol%) at room temperature in the presence of air. Progress of the reactions was monitored by TLC using *n*-hexane/ethyl acetate (8:1). After the reaction was completed the solvent was evaporated to give the crude product, which was purified by silica gel column chromatography employing *n*-hexane/ethyl acetate (8:1) as eluent.

General Procedure for the Synthesis of 2-Substituted Benzimidazoles in the Presence of a Catalytic Amount of CoxO-Co(salen) 11

For each reaction, a mixture of *o*-phenylendiamine **1** (1 mmol) and aldehyde **2** (1 mmol) was stirred in 5.0 mL of EtOH (96%) in the presence of catalyst (5 mol%) at room temperature. Progress of the reactions was monitored by TLC using *n*-hexane/ethyl acetate (8:1). After the reaction was completed the whole reaction mixture was directly passed through celite (porosity 4, capacity 50 mL) and rinsed with EtOH (3×15 mL). The recovered catalyst was dried and stored for another consecutive reaction run and the combined filtrates was concentrated by evaporating the solvent to give the crude product, which was purified by silica gel column chromatography employing *n*-hexane/ethyl acetate (8:1) as eluent.

Acknowledgements

We gratefully acknowledge the support of this work by the Shiraz University Research Council. We are also grateful to Mr. H. Sajedian Fard and Mr. M. S. Darvish Tafvizi for their helpful cooperation.

References

[1] a) M. J. Tebbe, W. A. Spitzer, F. Victor, S. C. Miller, C. C. Lee, T. R. Sattelberg Sr. , E. Mckinney, J. C. Tang, *J. Med. Chem.* **1997**, *40*, 3937; b) R. Trivedi, S. K. De, R. A. Gibbs, *J. Mol. Catal. A.* **2006**, *245*, 8.

[2] a) P. W. Erhardt, *J. Med. Chem.* **1987**, *30*, 231; b) B. E. Tomczuk, C. R. Taylor Jr. , L. M. Moses, D. B. Sutherland, Y. S. Lo, D. N. Johnson, W. B. Kinnier, B. F. Kilpatrick, *J. Med. Chem.* **1991**, *34*, 2993; c) A. A. Spasov,

I. N. Yozhitsa, L. I. Bugaeva, V. A. Anisimova, *Pharm. Chem. J.* **1999**, *33*, 232; d) P. N. Preston, *Chem. Heterocycl. Compd.* **1980**, *40*, 531; e) C. Zimmer, U. Wähnert, *Prog. Biophys. Mol. Biol.* **1986**, *47*, 31; f) G. L. Gravatt, B. C. Baguley, W. R. Wilson, W. A. Denny, *J. Med. Chem.* **1994**, *37*, 4338; g) K.-J. Soderlind, B. Gorodetsky, A. K. Singh, N. Bachur, G. G. Miller, J. W. Lown, *Anticancer Drug Des.* **1999**, *14*, 19.

[3] As inhibitors of DNA topoisomerases, see: a) J. S. Kim, B. Gatto, C. Yu, A. Liu, L. F. Liu, E. J. LaVoie, *J. Med. Chem.* **1996**, *39*, 992; b) A. Y. Chen, C. Yu, B. Gatto, L. F. Liu, *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8131; c) J. M. Woynarowski, M. McHugh, R. D. Sigmud, T. A. Beerman, *Mol. Pharmacol.* **1989**, 35, 177.

[4] As HIV-reverse transcriptase inhibitors, see: T. Roth, M. L. Morningstar, P. L. Boyer, S. H. Hughes, R. W. Buckheit, C. J. Michejda, *J. Med. Chem.* **1997**, *40*, 4199.

[5] a) S. Lin, L. Yang, *Tetrahedron Lett.* **2005**, *46*, 4315; b) Y. Kawashita, N. Nakamichi, H. Kawabata, M. Hayashi, *Org. Lett.* **2003**, *5*, 3713; c) H. Sharghi, O. Asemani, R. Khalifeh, *Synth. Commun.* **2008**, *38*, 1128.

[6] a) Y. Bai, J. Lu, Z. Shi, B. Yang, *Synlett* **2001**, 544; b) E. Hasegawa, A. Yoneoka, K. Suzuki, T. Kato, T. Kitazume, K. Yanagi, *Tetrahedron* **1999**, *55*, 12957.

[7] a) M. R. Grimmet, in: *Comprehensive Heterocyclic Chemistry*, (Eds.: A. R. Katritzky, C. W. Rees, K. T. Potts), Pergamon Press, New York, **1984**, Vol. 5, p 457; b) J. B. Wright, *Chem. Rev.* **1951**, *48*, 396; c) R. W. Middleton, D. G. Wibberley, *J. Heterocycl. Chem.* **1980**, *17*, 1757; d) T. Hisano, M. Ichikawa, K. Tsumoto, M. Tasaki, *Chem. Pharm. Bull.* **1982**, *30*, 2996; e) J. D. Geratz, F. M. Stevens, K. L. Polakoski, R. F. Parrish, *Arch. Biochem. Biophys.* **1979**, *197*, 551.

[8] a) A. Czarny, W. D. Wilson, D. W. Boykin, *J. Heterocycl. Chem.* **1996**, *33,* 1393; b) R. R. Tidwell, J. D. Geratz, O. Dann, G. Volz, D. Zeh, H. Loewe, *J. Med. Chem.* **1978**, *21*, 613; c) T. A. Fairley, R. R. Tidwell, I. Donkor, N. A. Naiman, K. A. Ohemeng, R. J. Lombardy, J. A. Bentley, M. Cory, *J. Med. Chem.* **1993**, *36*, 1746.

[9] a) K. Bougrin, A. Loupy, M. Soufiaoui, *Tetrahedron* **1998**, *54*, 8055; b) G. V. Reddy, V. V. V. N. S. R. Rao, B. Narsaiah, P. S. Rao, *Synth. Commun.* **2002**, *32*, 2467; c) A. Ben-Alloum, S. Bakkas, M. Soufiaoui, *Tetrahedron Lett.* **1998**, *39*, 4481.

[10] a) P. K. Dubey, C. V. Ratnam, *Indian J. Chem. B* **1979**, *18*, 428; b) B. Yadagiri, J. W. Lown, *Synth. Commun.* **1990**, *20*, 955; c) Y. Bathini, K. E. Rao, R. G. Shea, J. W. Lown, *Chem. Res. Toxicol.* **1990**, *3*, 268; d) M. P. Singh, T. Joseph, S. Kumar, Y. Bathini, J. W. Lown, *Chem. Res. Toxicol.* **1992**, *5*, 597; e) R. S. Harapanhalli, L. W. McLaughlin, R. W. Howell, D. V. Rao, S. J. Adelstein, A. I. Kassis, *J. Med. Chem.* **1996**, *39*, 4804.

[11] a) E. Verner, B. A. Katz, J. R. Spencer, D. Allen, J. Hataye, W. Hruzewicz, H. C. Hui, A. Kolesnikov, Y. Li, C. Luong, A. Martelli, K. Radika, R. Rai, M. She, W. Shrader, P. A. Sprengeler, S. Trapp, J. Wang, W. B. Young, R. L. Mackman, *J. Med. Chem.* **2001**, *44*, 2753; b) S. Kumar, V. K. Kansal, A. P. Bhaduri, *Indian J. Chem. B* **1981**, *20*, 254.

[12] L.-H. Du; Y.-G. Wang, *Synthesis* **2007**, 675.

[13] V. Ravl, E. Ramu, K. Vijay, A. Srinivas Rao, *Chem. Pharm. Bull.* **2007**, 55, 1254.

[14] M. M. Heravi, S. Sadjadi, H. A. Oskooie, R. H. Shoar, F. F. Bamoharram, *Catal. Commun.* **2008**, *9*, 504.

[15] A. B. Allouma, K. Bougrinb, M, Soufiaoui, *Tetrahedron Lett.* **2003**, *44*, 5935.

[16] a) J. J. vanden Eynde, F. Delfosse, P. Lor, Y. van Haverbeke, *Tetrahedron* **1995**, *51*, 5813; b) K. J. Lee, K. D. Janda, *Can. J. Chem.* **2001**, *79*, 1556.

[17] H. Chikashita, S. Nishida, M. Miyazaki, Y. Morita, K. Itoh, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 737.

[18] F. Pätzold, F. Zeuner, T. H. Heyer, H. J. Niclas, *Synth. Commun.* **1992**, *22*, 281.

[19] I. Bhatnagar, M. V. George, *Tetrahedron* **1968**, *24*, 1293.

[20] F. F. Stephens, J. D. Bower, *J. Chem. Soc.* **1949**, 2971.

[21] P. L. Beaulieu, B. Hache, E. Von Moos, *Synthesis* **2003**, 1683.

[22] a) M. A. Weidner-Wells, K. A. Ohemeng, V. N. Nguyen, S. Fraga-Spano, M. J. Macielag, H. M. Werblood, B. D. Foleno, G. C. Webb, J. F. Barrett, D. J. Hlasta, *J. Bioorg. Med. Chem. Lett.* **2001**, *11*, 1545; b) S. C. Austen, J. M. Kane, *J. Heterocycl. Chem.* **2001**, *38*, 979.

[23] K. Bahrami, M. M. Khodaei, I. Kavianinia, *Synthesis* **2007**, *4*, 547.

[24] G. Navarrete-Vázquez, H. Moreno-Diaz, F. Aguirre-Crespo, I. León-Rivera, R. Villalobos-Molina, O. Muñoz-Muñiz, S. Estrada-Soto, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4169.

[25] C. Baleizão, H. Garcia, *Chem. Rev.* **2006**, *106*, 3987.

[26] a) C. Baleizão, B. Gigante, H. Garcia, A. Corma, *Tetrahedron* **2004**, *60*, 10461; b) A. R. Silva, C. Freire, B. de Castro, *Carbon* **2004**, *42*, 3027; c) C. Baleizão, B. Gigante, H. Garcia, A. Corma, *J. Catal.* **2004**, *221*, 77; d) A. R. Silva, V. Budarin, J. H. Clark, B. de Castro, C. Freire, *Carbon* **2005**, *43*, 2096.

[27] T. Katsuki, *J. Mol. Catal. A* **1996**, *113*, 87.

[28] K. Maruyama, T. Kusukawa, T. Mashino, A. Nishinaga, *J. Org. Chem.* **1996**, *61*, 3342.

[29] S. E. Schaus, J. Bránalt, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 403.

[30] Y. Belokon, M. Flego, N. Ikonnikov, M. Moscalenko, M. North, C. Orizu, V. Tararov, M. Tasinazzo, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1293.

[31] H. Sharghi, H. Naeimi, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1525.

[32] a) H. Sharghi, M. A. Nasseri, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 137; b) M. Shamsipur, M. Yousefi, M. Hosseini, M. R. Ganjali, H. Sharghi, H. Naeimi, *Anal. Chem.* **2001**, *73*, 2869; c) M. Shamsipur, A. Soleymanpour, M. Akhond, H. Sharghi, M. A. Naseri, *Anal. Chem. Acta* **2001**, *450*, 37; d) M. Shamsipur, M. Najafi, M. R. Milani Hosseini, H. Sharghi, *Electroanalysis* **2007**, *19*, 1661; e) S. Sadeghi, A. Gafarzadeh, M. A. Naseri, H. Sharghi, *Sens. Actuators B: Chemical* **2004**, *98*, 174; f) M. Shamsipur, A. R. Ghiasvand, H. Sharghi, H. Naeimi, *Anal. Chim. Acta* **2000**, *408*, 271; g) N. Alizadeh, S. Ershad, H. Naeimi, H. Sharghi, M. Shamsipur, *Fresenius J. Anal. Chem.* **1999**, *365*, 511.

[33] J. L. Figueiredo, M. F. R. Pereira, M. M. A. Freitas, J. J. M. O′rfaõ, *Carbon* **1999**, *37*, 1379.

[34] a) G. Lombardi, *For Better Thermal Analysis. International Confederation for Thermal Analysis*, Univ. of

Rome, Italy, **1980**; b) E. Paterson, R. Swarffield, *Thermal Analysis,* in: *A Handbook of Determinative Methods in Clay Mineralogy*, (Ed.: M. J. Wilson), Chapman and Hall, New York, **1987**.
[35] a) S. P. Chan, G. Chen, X. G. Gong, Z. F. Liu, *Phys. Rev. Lett.* **2003**, *90*, 86403; b) X. S. Shajan, C. Mahadevan, *Cryst. Res. Technol.* **2005**, *40*, 598.
[36] P. Selvarajan, B. N. Das, H. B. Gon, K. V. Rao, *J. Mater. Sci. Lett.* **1993**, *12*, 1210.
[37] M. T. Postek, D. C. Joy, *J. Res. Natl. Bur. Stand.* **1987**, *92*, 205.
[38] A. D. L. Humphris, M. J. Miles, J. K. Hobbs, *Appl. Phys. Lett.* **2005**, *86*, 34106.
[39] Y. V. Basova, D. D. Edie, P. Y. Badheka, H. C. Bellam, *Carbon* **2005**, *43*, 1533.
[40] M. Fleischer, L. J. Cabri, G. Y. Chao, A. Pabst, *Am. Mineral.* **1980**, *65*, 1065.
[41] M. P. Singh, S. Sasmal, W. Lu, M. N. Chatterjee, *Synthesis* **2000**, *10*, 1380.
[42] Y. Li, M. A. Trush, *Arch. Biochem. Biophys.* **1993**, *300*, 346.

