An effective lactic acid-modified $H\beta$ zeolite for synthesis of bis(indolyl)methanes

Guo Yi Bai · Zheng Ma · Lingjuan Shi · Tianyu Li · Jie Han · Guofeng Chen · Na Li · Peide Liu

Received: 6 April 2012/Accepted: 19 April 2012/Published online: 11 May 2012 © Springer Science+Business Media B.V. 2012

Abstract Excellent activity and stability have been observed for a lactic acidmodified H β (LA-H β) zeolite in the synthesis of bis(indolyl)methanes by Friedel– Crafts alkylation of indole with aldehydes. It is proposed that lactic acid treatment is appropriate for dealumination of H β zeolite, and results in a LA-H β zeolite with greater surface area, fewer weak acid sites, and more moderately-strong acid sites, as confirmed by the Brunauer–Emmett–Teller method, inductively coupled plasma emission spectrometry, and temperature-programmed desorption of NH₃. Moreover, both electronic and steric effects of substituents on the aromatic ring of the aldehydes were found to be important in this reaction.

Keywords H β zeolite · Lactic acid modification · Bis(indolyl)methanes · Synthesis · Stability

Introduction

Indoles and their derivatives are important heterocyclic compounds that have been widely used in pharmaceuticals and synthetic chemistry [1, 2]. Among a variety of indole analogs, bis(indolyl)methanes, in particular, have attracted much interest in recent years because of their novel structures and important biological activity, for example antibacterial, anticancer, and insecticidal activity [3–5]. Bis(indolyl)methanes are usually obtained by Friedel–Crafts alkylation of indole with aldehydes or ketones in the presence of either Lewis or protic acids [6–8]. However, these traditional catalysts have limitations, for example environmental pollution hazards

Key Laboratory of Chemical Biology of Hebei Province, College of Chemistry and Environmental Science, Hebei University, No.180 Wusi East Road, Baoding 071002, Hebei, People's Republic of China

e-mail: baiguoyi@hotmail.com

G. Y. Bai (🖂) · Z. Ma · L. Shi · T. Li · J. Han · G. Chen · N. Li · P. Liu

arising from the disposal of potentially toxic wastes, reactor corrosion, and handling difficulties. Therefore, because of the increasing demand for environmental protection, research on this reaction has increasingly focused on use of solid acid catalysts [9–11].

Zeolites, with the advantages of selective adsorption, high strength, and thermal stability, are regarded as an optimum choice among all solid acid catalysts [12, 13]. Results have been reported for the synthesis of bis(indolyl)methanes over zeolites [14–16]. For example, Reddy et al. investigated the synthesis of bis(indolyl)methanes over HY zeolite catalysts, and reported relatively good activity and reusability [14]. Karthik et al. reported that ZnY zeolites were more active than the parent Y zeolite in the synthesis of bis(indolyl)methanes [15]; loss of Zn, however, is a potential threat to the environment. Acid modification has been proved to be important for improving the activity of parent zeolites [17–20]. For example, Srivastava et al. reported that a tartaric acid-modified H β zeolite was an efficient catalyst for acylation and esterification of aromatic compounds [20].

As part of our continuing interest in the development of an effective method for synthesis of heterocyclic compounds of biological importance [21], we report a recent study of the synthesis of bis(indolyl)methanes by condensation of indole, over zeolites, with a variety of aldehydes. Synthesis of bis(indolyl)phenylmethane was chosen as model reaction and a lactic acid-modified H β (LA-H β) zeolite was found to have the best catalytic performance in this reaction. The activity and stability of the modified and parent H β zeolites were investigated and their structures were well characterized.

Experimental

Catalyst preparation

Unless otherwise stated, all chemicals were purchased from Baoding Huaxin Reagent and Apparatus and were used without further purification. Lactic acid modified H β zeolite was prepared by impregnating 1 g parent H β zeolite (Tianjin Chemist Catalyst) in 25 mL of an aqueous solution of 1.0 mol/L lactic acid at 80 °C for 1 h. The zeolite was then dried at 130 °C and calcined at 550 °C for 4 h. The prepared catalyst was denoted LA-H β . Tartaric acid, phosphoric acid, and oxalic acid-modified H β and MCM-41 zeolites were also prepared by the same method and denoted TA-H β , PA-H β , OA-H β , TA-MCM-41, PA-MCM-41, and OA-MCM-41, respectively.

Catalyst characterization

X-ray diffraction (XRD) analysis was performed on a Bruker D8 advance diffractometer with Cu Ka radiation. Bulk compositions were identified by inductively coupled plasma analysis (ICP) on a Thermo Vista-MPX spectrometer. The Brunauer–Emmett–Teller (BET) surface area and total pore volume were determined by use of a Micromeritics Tristar II 3020 surface area and pore analyzer.

Temperature-programmed desorption of NH_3 (NH_3 -TPD) experiments were conducted on a TP-5000 instrument from Xianquan.

Catalyst activity test

Bis(indolyl)methanes (Scheme 1) were synthesized in a round-bottomed flask. In a typical run, 2 mmol indole, 1 mmol aldehyde, and 2 mL dichloromethane were placed in the flask and heated to 30 °C. Then, 0.15 g zeolite was added and the reaction continued at this temperature for 6 h with stirring. The resulting reaction mixture was analyzed by high-performance liquid chromatography (HPLC) on a silica gel column (250 mm \times 4.6 mm) with cyclohexane–isopropanol 95:5 (*v*/*v*) as mobile phase at 0.6 mL/min constant flow. The identities of the products were confirmed by use of LC–MS (Agilent G6300) and ¹H NMR (Bruker Avance III 600 MHz).

Results and discussion

Catalyst selection and characterization

Because indole is not active in the Friedel–Crafts alkylation in the absence of a catalyst, selection of a suitable catalyst is crucial to efficient synthesis of bis(indolyl)phenylmethane. Commercial zeolites were examined first (Table 1, entries 1–4). It is clear that both H β zeolite and MCM-41 zeolite had high activity in this reaction. Yields of bis(indolyl)phenylmethane were >65 % over both H β zeolite and MCM-41 zeolite, but still below our expectation. Considering the benefit of acid modification, a series of acid modified H β zeolites and MCM-41 zeolites were then prepared and investigated (Table 1, entries 5–12). As expected, the acid-modified H β zeolites had better catalytic performance than the parent H β zeolite, especially for the LA-H β zeolite. Conversion of benzaldehyde and selectivity for bis(indolyl)phenylmethane were 90 and 97.4 % respectively over the LA-H β zeolite, whereas catalytic performance of the acid-modified MCM-41 zeolites was no better than that of the parent MCM-41 zeolite. Thus, LA-H β zeolite was proved



R = chloro, nitro, hydroxyl group, *etc*.



Table 1Catalytic results in the synthesis of bis(indolyl)phenylmethane over different zeolitesReaction conditions: indole-to- benzaldehyde molar ratio, 3:1; amount of catalyst, 0.2 g; reaction temperature, 25 °C;	Zeolite	Conversion of benzaldehyde (%)	Selectivity for bis(indolyl) phenylmethane (%)		
	Нβ	68.3	96.3		
	HY	28.6	66.5		
	ZSM-5	26.9	64.5		
	MCM-41	87.7	86.1		
	$TA-H\beta$	84.9	97.7		
	$PA-H\beta$	79.7	96.1		
	$OA-H\beta$	73.6	94.5		
	$LA-H\beta$	90.0	97.4		
	TA-MCM-41	66.4	89.5		
	PA-MCM-41	73.8	89.4		
	OA-MCM-41	61.2	87.7		
	LA-MCM-41	81.3	91.0		

reaction time. 3 h



Fig. 1 XRD patterns of H β (*a*) and LA-H β (*b*) zeolites

to have the highest activity and was, therefore, chosen as the catalyst for further investigation.

The zeolites were characterized to correlate their activity with their structures. The XRD patterns of H β and LA-H β zeolite are given in Fig. 1. The characteristic diffraction peaks of LA-H β zeolite were at approximately 7.5° and 22.5°, similar to those of the parent H β zeolite, indicating that no obvious structural changes occur as a result of the acid treatment. Furthermore, we found that the crystallinity of LA-H β zeolite decreased slightly as a result of lactic acid modification; this was ascribed to dealumination of the zeolite, probably because of removal of aluminium species from the lattice by complexation of an aluminium ion by a lactate ion and water ligands. The Si/Al molar ratios of H β and LA-H β zeolites were therefore calculated

Table 2 Textural properties of $H\beta$ and LA- $H\beta$ zeolites	Zeolite	Si/Al	BET (m ² /g)	Pore volume (cm^3/g)
	Hβ	12.1	431	0.29
	$LA-H\beta$	20.9	469	0.30



Fig. 2 NH₃-TPD profiles of H β (*a*) and LA-H β (*b*) zeolites (A: original results, B: curve-fitting results)

from the ICP results, and are listed in Table 2. The results indicate that the Si/Al molar ratio increased from 12.1 to 20.9 after lactic acid modification, and thus dealumination of the zeolite was proved, in accordance with previous results [20, 22]. The nitrogen-adsorption results for H β and LA-H β zeolites are also listed in Table 2. It is obvious that the BET surface area of the zeolites increased from

Zeolite	Amounts of acid ^a					
	Weak acid	Moderately-strong acid	Strong acid	Total acids		
Нβ	1.9	0.6	0.2	2.7		
LA-H β	1.2	0.7	0.3	2.2		

Table 3 Amounts of acid in the H β and LA-H β zeolites

^a Relative concentrations calculated from the NH₃-TPD results

Table 4 Stability of LA-H β zeolite	LA-H β zeolite	Conversion of benzaldehyde (%)	Selectivity for bis(indolyl) phenylmethane (%)	
	Fresh	99.4	97.2	
	Regenerated first cycle	99.0	96.3	
Reaction conditions: indole-to- benzaldehyde molar ratio, 2:1; amount of catalyst, 0.15 g; reaction temperature, 30 °C; reaction time, 6 h	Regenerated second cycle	99.2	96.4	
	Regenerated third cycle	99.8	97.7	
	Regenerated fourth cycle	99.5	96.3	
	Regenerated fifth cycle	99.1	95.0	

431 m²/g to 469 m²/g and the pore volume increased slightly after acid modification; this also can be attributed to dealumination during the modification process which, in turn, increased the activity of the LA-H β zeolite.

NH₃-TPD analyses have been widely used to determine the number and type of acid sites available on the surface of catalysts by measurement of the amounts of NH₃ desorbed at different temperatures. NH₃-TPD testing of H β and LA-H β was conducted, and the results are illustrated in Fig. 2. There is only one large peak, centered at approximately 250 °C, in the NH₃ desorption profile of the parent H β zeolite, whereas there are two peaks at approximately 260 and 420 °C in the NH₃ desorption profile of LA-H β zeolite (Fig. 2A). According to curve-fitting results for the NH₃-TPD profiles (Fig. 2B), three NH₃ desorption peaks were confirmed in the range 150–350 °C (T₁), 350–500 °C (T₂), and 500–650 °C (T₃), respectively [23]. It was obvious that the number of weak acid sites decreased substantially after lactic acid modification whereas the number of moderately-strong acid sites and strong acid sites increased slightly (Table 3). Furthermore, after acid modification the NH₃ desorption peaks shifted toward higher temperatures and total amounts of desorbed NH₃ decreased. Thus, it is suggested that fewer weak acid sites and more moderately-strong acid sites resulted from the transformation.

Stability of LA-H β zeolite

After initial optimization of the reaction conditions to improve the activity of LA-H β zeolite, stability testing was performed under the optimum reaction conditions (Table 4). Because carbonaceous deposition was proved, in our previous work, to be the main reason for zeolite deactivation [19], regenerated LA-H β zeolite was



Table 5 contin

Table 5 continued	Aldehyde	Conversion of aldehyde (%)	Selectivity for bis(indolyl) methane (%)
	СНО	52.9	91.6
	СНО	69.2	90.8
	H ₃ C CH ₃		
	СНО	34.7	70.7
Reaction conditions: indole-			
to-aldehyde molar ratio, 2:1; amount of catalyst, 0.15 g; reaction temperature, 30 °C; reaction time, 6 h	ОН		

obtained after further calcination at 550 °C for 4 h. It was found that the regenerated catalyst retained excellent catalytic activity in five subsequent cycles. Conversion of benzaldehyde remained above 99 %, and selectivity for bis(indolyl)phenylmethane was up to 95 % during the whole test. Thus, LA-H β zeolite was proved to have good stability in this reaction.

Synthesis of bis(indolyl)methanes

Finally, a series of aldehydes was examined with indole in the presence of LA-H β zeolite under the same reaction conditions. The corresponding bis(indolyl)methanes were obtained in moderate to excellent yields, as shown in Table 5. Reactions of substrates with mono electron-withdrawing groups proceeded well, with conversion of the aldehydes always >92 %, whereas conversion was clearly lower for aldehydes with electron-donating groups. Thus, electronic effects seem to be prominent in this reaction, a result which is in harmony with the rules of electrophilic aromatic substitution. Steric effects on the benzene ring were also observed. 2,6-Dichlorobenzaldehyde was found to result in rather lower conversion than 2,4-dichlorobenzaldehyde, suggesting that steric factors are also important in this reaction.

Conclusions

In conclusion, the effective synthesis of bis(indolyl)methanes by Friedel–Crafts alkylation of indole with aldehydes over zeolites was successfully achieved in the work discussed in this paper. A LA-H β zeolite was found to have the best activity among the zeolites studied, because of its larger surface area, fewer weak acid sites, and more moderately-strong acid sites. Furthermore, the LA-H β zeolite is readily recyclable and can be used five times without any loss of catalytic activity. Thus, this effective process involving a LA-H β zeolite is not only economically viable but also potentially applicable to large-scale reactions.

Acknowledgments Financial support by the National Natural Science Foundation of China (20806018), the Natural Science Foundation of Hebei Province (B2011201017), and the Science Project of the Hebei Education Department (ZD200910) are gratefully acknowledged.

References

- 1. Y.F. Du, R.H. Liu, G. Linn, K. Zhao, Org. Lett. 8, 5919 (2006)
- H.J. Wadsworth, B. Shan, D. O'shea, J.M. Passsmore, W.J. Trigg, A. Ewan, US Patent 0020884 (2012)
- G. Giannini, M. Marzi, M.D. Marzo, G. Battistuzzi, R. Pezzi, T. Bruneti, W. Cabri, L. Vesci, C. Pisano, Bioorg. Med. Chem. Lett. 19, 2840 (2009)
- 4. S. Safe, S. Papineni, S. Chintharlapalli, Cancer Lett. 269, 326 (2008)
- 5. M. York, M. Abdelrahim, S. Chintharlapalli, S.D. Lucero, S. Safe, Clin. Cancer Res. 13, 6743 (2007)
- 6. G. Babu, N. Sridhar, P.T. Perumal, Synth. Commun. 30, 3609 (2000)
- 7. B.V. Gregorvich, K.S.Y. Liang, D.M. Clugston, S.F. Macdonald, Can. J. Chem. 46, 3291 (1968)
- 8. M.W. Roomi, S.F. Macdonald, Can. J. Chem. 48, 139 (1970)
- 9. C. Ramesh, J. Banerjee, R. Pal, B. Das, Adv. Synth. Catal. 345, 557 (2003)
- 10. H. Firouzabadi, N. Iranpoor, M. Jafarpour, A. Ghaderi, J. Mol. Catal. A Chem. 253, 249 (2006)
- 11. H. Firouzabadi, N. Iranpoor, A.A. Jafari, J. Mol. Catal. A Chem. 244, 168 (2006)
- 12. K. Bachari, R. Chebout, R.M. Guerroudj, M. Lamouchi, Res. Chem. Intermed. 38, 367 (2012)
- P.P. Pescarmona, B.C. Gagea, P. Van der Aa, P.A. Jacobs, J.A. Martens, Catal. Today 159, 120 (2011)
- A.V. Reddy, K. Ravinder, V.L.N. Reddy, T.V. Goud, V.Y. Ravikanth, Y. Venkateswarlu, Synth. Commun. 33, 3687 (2003)
- M. Karthik, A.K. Tripathi, N.M. Gupta, M. Palanichamy, V. Murugesan, Catal. Commun. 5, 371 (2004)
- M. Karthik, C.J. Magesh, P.T. Perumal, M. Palanichamy, B. Arabindoo, V. Murugesan, Appl. Catal. A Gen. 286, 137 (2005)
- 17. Y. Fan, X.J. Bao, X.Y. Lin, G. Shi, H.Y. Liu, J. Phys. Chem. B 110, 15411 (2006)
- 18. M.R. Apelian, A.S. Fung, G.J. Kennedy, T.F. Degnan, J. Phys. Chem. 100, 16577 (1996)
- G.Y. Bai, Y.H. Yang, Z. Ma, J.Z. Xu, M.D. Qiu, F. He, X.L. Yan, H.Y. Dou, Res. Chem. Intermed. 38, 795 (2012)

- 20. R. Srivastava, N. Iwasa, S.I. Fujita, M. Arai, Catal. Lett. 130, 655 (2009)
- 21. G.Y. Bai, K. Xu, G.F. Chen, Y.H. Yang, T.Y. Li, Synthesis 10, 1599 (2011)
- 22. Z.K. Xie, Q.L. Chen, C.F. Zhang, J.Q. Bao, Y.H. Cao, J. Phys. Chem. B 104, 2853 (2000)
- 23. D.F. Jin, B. Zhu, Z.Y. Hou, J.H. Fei, H. Lou, X.M. Zheng, Fuel 86, 2707 (2007)