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Synthesis of 2-methylpiperazine by photocatalytic reaction in a non-aqueous suspension of semiconductor–zeolite composite catalysts†

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UV irradiation onto a non-aqueous suspension of semiconductor–zeolite composite catalysts with *N*-(β-hydroxypropyl)ethylenediamine (N-β-HPEDA) produces 2-methylpiperazine and piperazine. The yield of 2-methylpiperazine and piperazine depends on the type of semiconductor and zeolite. A 5 wt% TiO_2–Hβ composite photocatalyst shows highest yield of 2-methylpiperazine.

Introduction

The chemistry of heterocyclic compounds is one of the interesting branches of organic chemistry because of the diversity of synthetic procedures, and the physiological and industrial significance of heterocyclic compounds. Synthesis of saturated cyclic amines such as piperazine and its derivatives is an important reaction because of the various uses of these compounds as anthelminitics, perfumes and starting materials in pharmaceutical and agrochemical industries. Although several methods[1] are now available for their synthesis, the importance of these molecules has provided the impetus to develop more convenient procedures. Selective production of these compounds comprises cyclization, dehydrogenation and dehydration reactions. A great variety of chemical transformations in the presence of semiconductor powders (CdS and TiO_2) or colloids has been reported and summarized in recent review articles.[2–5] However, in spite of several semiconductor-mediated reactions, examples of inter and intramolecular cyclizations are rather limited in the literature.[6–8] In continuation of our work on the synthesis of heterocyclic compounds[9–12] we have found that use of zeolite catalysts is attractive because they are inexpensive, reusable, and have potential industrial application.

Herein, we have investigated a novel, convenient and eco-friendly intramolecular cyclization of *N*-(β-hydroxypropyl)-ethylenediamine in the presence of a variety of semiconductor–zeolite catalysts and molecular oxygen. To the best of our knowledge, this paper describes for the first time the synthesis of 2-methylpiperazine using photocatalysis.

Experimental

The semiconductor–zeolite composite catalysts were prepared by thorough mechanical mixing of 2 and 5 wt% of cadmium(II) sulfide (CdS, Aldrich), TiO_2 (P25, 80% anatase and 20% rutile, with a surface area of 50 m^2 g^{-1} from Degussa Corporation) and ZnO (Fluka, 99%) in an agate mortar and pestle with commercial zeolite powders of HZSM-5 (SiO_2–Al_2O_3 = 30; PQ Corporation, USA), HY (SiO_2–Al_2O_3 = 4.4; Conteka, Sweden) and Hβ (SiO_2–Al_2O_3 = 30; SÜD CHEMIE AG, Germany). A non-aqueous (acetonitrile, 20 ml) solution of 0.1 mmol of N-β-HPEDA[13] and catalyst (100 mg) was placed in a round bottomed quartz photoreactor and irradiated with a 250 W HP mercury lamp (Philips, India) with magnetic stirring (1200 rpm) for 12 h under a constant stream of molecular oxygen (20 ml h^{-1}). Thin layer chromatography (TLC) was performed in CH_3OH–$CHCl_3$ (10 : 90) solvent system to detect the product spots. Products were isolated by column chromatography and confirmed with C, H, N analysis, melting point, ^{1}H-NMR, and EI-MS.

Results and discussion

Table 1 shows the representative results of photocatalytic reaction of non-aqueous *N*-(β-hydroxypropyl)ethylenediamine solution by various types of semiconductor–zeolite composite catalysts. Although the photocatalytic reaction with all the semiconductor–zeolite catalysts gave 2-methylpiperazine **1**, the demethylated piperazine **2** was also observed. On the other hand, photocatalyzed reactions with only semiconductor did not yield the products **1** or **2**. It has been shown that the reaction is *photocatalytic* as this reaction requires the presence of photoirradiation, oxygen and catalyst. As observed from our earlier experiments[10–11] no product was formed in the presence of bare zeolite. As clearly seen in Table 1, the ratios of **1** and **2** depend on the nature and type of the zeolite supports. All the semiconductor–zeolites were found to promote the reaction and product formation always favored **1**. Zeolites modified with semiconductors ZnO and CdS were not very effective at acceleration of the reaction. In contrast, zeolites modified with titanium dioxide considerably facilitated the intramolecular cyclization. Increase in the amount of semiconductor (TiO_2, ZnO and CdS) loading on zeolites (>5%) did not give better results. In this study, one of the best photocatalysts for the production of **1** (major product) was found to be 5 wt% TiO_2–Hβ. It was found that moderate hydrophobicity and acid site strength of the semiconductor–zeolite composite favour the cyclization reaction. Also the structure of the Hβ–zeolite may help to attain the maximum yield of **1** and **2**, as it is known that Hβ is a combination of both HZSM-5 (channel pore system, high Si–Al ratio) and Y (12-ring pore system) zeolites. There was no change observed in the physical properties of the semiconductor–zeolite catalysts, and XRD analysis (results not shown) confirms that crystallanity in the zeolites is not reduced

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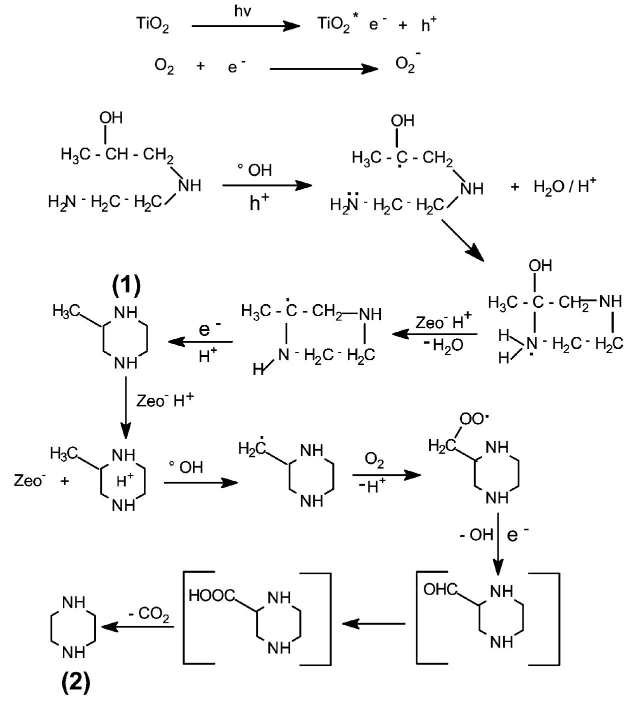
Table 1 Results on photocatalytic cyclization of (N-β-HPEDA) by semiconductor–zeolite composite catalysts[a]

Catalyst	Surface area[b] /m^2 g^{-1}	Acidity[c]/mmol g^{-1}	Yield[e] of 2-methylpiperazine (%)	Yield[e] of piperazine (%)
2 wt% TiO_2–HZSM-5 (30)	350	0.37	20.8	8.50
5 wt% TiO_2–HZSM-5 (30)	320	0.32	23.5	10.6
2 wt% TiO_2–HY (4.4)	400	0.25	22.9	12.3
5 wt% TiO_2–HY (4.4)	341	0.20	24.8	13.9
2 wt% TiO_2–Hβ (30)	495	0.43	26.9	13.6
5 wt% TiO_2–Hβ (30)	485	0.47	31.9	14.8
2 wt% ZnO –HZSM-5 (30)	326	0.13	8.60	7.54
5 wt% ZnO–HZSM-5 (30)	320	0.15	10.6	8.20
2 wt% ZnO–HY (4.4)	336	0.18	11.6	8.53
5 wt% ZnO–HY (4.4)	300	0.21	12.9	7.68
2 wt% ZnO–Hβ (30)	490	0.41	13.5	9.03
5 wt% ZnO–Hβ (30)	483	0.40	14.9	10.5
2 wt% CdS–HZSM-5[d] (30)	356	0.45	14.6	6.50
5 wt% CdS–HZSM-5 (30)	349	0.49	16.9	9.54
2 wt% CdS–HY (4.4)	409	0.31	19.5	11.5
5 wt% CdS–HY 4.4)	389	0.36	20.5	12.6
2 wt% CdS–Hβ(30)	468	0.33	21.6	13.5
5 wt% CdS–Hβ(30)	459	0.37	23.0	14.9
TiO_2	50	—	—	—
ZnO	30	—	—	—
CdS	—	—	—	—
Zeolite	—	—	—	—

[a] All the reactions were carried out by stirring a mixture of N-β-HPEDA (0.1 mmol), acetonitrile (20 ml), catalyst (100 mg) and constant stream of molecular oxygen (20 ml h^{-1}) under irradiation with 250 W HP mercury lamp for 12 h. [b] BET technique measured with liquid N_2 at 77 K. [c] Temperature Programmed Desorption of NH_3 measured on AutoChem 2910 (Micromeritics, USA). [d] All the semiconductor–zeolite catalysts were calcined at 400 °C for 6 h except for CdS–zeolite catalysts. [e] Isolated yields

by modification and/or reaction. To the best of our knowledge, no report has previously been observed for the intramolecular cyclization of *N*-(β-hydroxypropyl)ethylenediamine on semiconductor–zeolite catalysts at ambient temperature by photocatalysis.

The assumed reaction mechanism is depicted in Scheme 1. As the reaction requires the presence of a photocatalyst, it can be deduced that oxidation and/or reduction processes are involved. From rate constants of the reaction of ˙OH with propan-2-ol[14] it can be assumed that the most oxidizable site on *N*-(β-hydroxypropyl)ethylenediamine will be the hydrogen atom on the tertiary carbon. The resulting radical is expected to cyclize on the amine group by catalytic dehydration on the zeolite. The main photoproduct, 2-methylpiperazine **1**, results from the reduction of the intermediate radical. As elimination of the methyl group occurs, it can be assumed that the ring is protected against oxidation by protonation with the zeolites which have acidic properties. Also it has been well documented that zeolite catalysts can stabilize the reactive intermediates in several photochemical reactions.[15] Thus the oxidation on the methyl group of 2-methylpiperazine becomes more selective. It is likely that intermediate aldehydes and acids are formed, but they cannot be observed, since it was proved in our experimental conditions that these intermediates are phototransformed into piperazine **2**.[16]



Scheme 1 Assumed reaction mechanism for the formation of 2-methylpiperazine and piperazine.

In conclusion, we have succeeded in the one step synthesis of 2-methylpiperazine and piperazine which are useful materials for various fine chemicals and pharmaceuticals from *N*-(β-hydroxypropyl)ethylenediamine by the ambient temperature photocatalytic reaction of semiconductor–zeolite composite catalysts. The present results potentially provide a new mode of photocatalytic synthetic application for *N*-heterocyclic compounds. This reaction offers advantages to the synthetic chemist interested in inter and intramolecular cyclizations over the alternative methods of preparation and contribute to the ecological synthesis of highly specialized products.

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13 N-β-HPEDA has been prepared with slow and dropwise addition of 1,2-propylene oxide (342 g) through a separating funnel to 544 g of ethylenediamine dissolved in 2 litres of methanol and contained in a 5-litre, 3-necked flask fitted with a stirrer and a reflux condenser. The temperature was kept at 40–50 °C by a water bath. A period of three hours was required for the addition of the 1,2-propylene oxide. The product, a transparent slightly viscous liquid with a mild ammoniacal odour, was obtained by fractional distillation (C, H, N data for $C_5H_{14}N_2O$: Calculated: C = 50.84, H = 11.86, N = 23.72; Found: C = 50.75, H = 11.95, N = 23.70%).

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16 **2-Methylpiperazine**: ^{1}H-NMR (200 MHz, D_2O) δ 0.95 (d, 3H, J = 6.9 Hz), 2.25 (t, 1H, J = 7 Hz), 2.58 (t, 1H, J = 7 Hz), 2.65–2.75 (m, 2H), 2.80–2.85 (m, 3H); C, H, N data for $C_5H_{12}N_2$: Calculated = 60.0, 12.0, 28.0; Found = 60.10, 11.83, 27.97%; MS-EI (*m*/*z*) 100 (M^+); mp = 65–67 °C. **Piperazine**: ^{1}H-NMR (200 MHz, D_2O) δ 2.79 (s, 8H); C, H, N data for $C_4H_{10}N_2$: Calculated = 55.81, 11.62, 32.55; Found = 55.70, 11.72, 32.52; MS-EI (*m*/*z*) 86 (M^+); mp = 108–110 °C.