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# Solvent Free *N*-Heterocyclization of Primary Amines to *N*-Substituted Azacyclopentanes Using Hydrotalcite as Solid Base Catalyst

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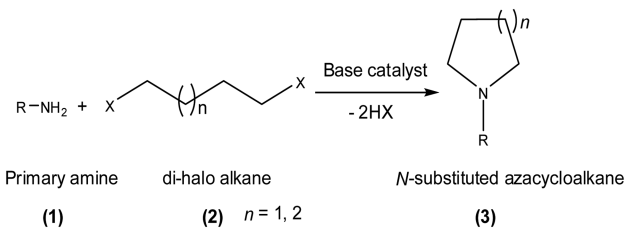
An ecofriendly catalytic route for selective synthesis of *N*-substituted azacyclopentanes, nitrogen-containing heterocyclic intermediates for many bioactive compounds, was established by carrying out *N*-heterocyclization (di *N*-alkylation) of primary amines with 1,4-dichloro butane (as dialkylating agent) using catalytic amount of hydrotalcite as solid base catalyst. The hydrotalcite was found to be efficient solid base catalyst for di *N*-alkylation of different primary amines (aniline, benzyl amine, cyclohexyl amine and *n*-butyl amine) giving 82 to 96% conversion (at optimized reaction condition) of 1,4-dichloro butane and > 99% selectivity of respective *N*-substituted azacyclopentanes within 30 min. under solvent free condition. The reaction parameters significantly influence the conversion of 1,4-dichloro butane to *N*-substituted azacyclopentanes. The nature of substituent present on amino group affects the reactivity of amine substrates for di *N*-alkylation reaction with 1,4-dichloro butane. The 1,4-dichloro butane was found to be highly reactive alkylating agent for di *N*-alkylation of amines as compared to 1,4-dihydroxy butane. The reusability of the catalyst and its chemical stability in the reaction was demonstrated.

**Key Words :** *N*-Substituted azacycloalkanes, *N*-Heterocyclization, Amines, Solid base, Hydrotalcite

## Introduction

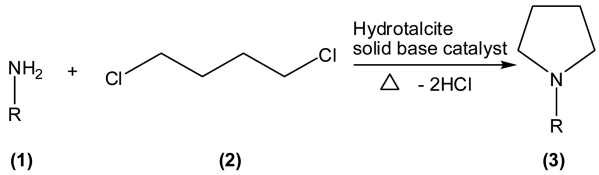
Heterocyclics constitute the largest group of organic compounds of great interest as they are building blocks of several natural products like alkaloids, hormones, vitamins, antibiotics, pharmaceuticals, dyes, agrochemicals, *etc*.[1,2] The *N*-substituted azacycloalkanes are nitrogen-containing heterocyclics, which are intermediates for many natural products and bioactive compounds. Usually, *N*-substituted azacycloalkanes are prepared by alkylation of primary amines with glycol disulfonate in anhydrous dioxane under refluxed condition,[3] multistep reactions of benzaldehyde and 3-bromopropylamine hydrobromide,[4] *N*-phenylation of amines,[5] metal complex catalyzed coupling reactions,[6,7] *etc*. The major drawbacks of these methods for the synthesis of *N*-substituted azacycloalkanes include harsh reaction conditions, use of hazardous solvents and expensive homogenous catalysts having problem of separation and reuse. The base catalyzed di *N*-alkylation (*N*-heterocyclization) of primary amines (**1**) with di-halo alkanes (**2**) also result to *N*-substituted azacycloalkanes (**3**) (Scheme 1).




**Scheme 1.** Synthesis of *N*-substituted azacycloalkane by base catalyzed di *N*-alkylation of primary amines with dihalo alkanes.

A number of *N*-substituted (alkyl and aryl) azacycloalkanes have been synthesized by microwave assisted base ($K_2CO_3$) catalyzed aqueous *N*-heterocyclization/di *N*-alkylation of primary amines with di-halo alkanes (as dialkylating agent) in excellent yield.[8,9] However, this method is not industrially viable due to use of equimolar quantity of homogeneous base catalyst ($K_2CO_3$) in aqueous medium generating huge amount of alkaline waste and difficult handling of microwave reaction system for large scale production. Therefore, it is of great interest to develop economically viable and environmentally more benign synthetic route for *N*-heterocyclization/di *N*-alkylation to synthesize *N*-substituted azacycloalkanes.

Hydrotalcites are layered double hydroxides,[10] which have been reported to be used as ion exchangers,[11] additives for polymers,[12] sorbents,[13] drug delivery agents,[14] catalysts or catalyst supports.[15-21] These materials have recently received much attention as potential solid base catalysts or catalyst




R = Phenyl, Benzyl, Cyclohexyl, *n*-butyl.

**Scheme 2.** Synthesis of *N*-substituted azacyclopentanes by hydrotalcite catalyzed di *N*-alkylation of primary amines with 1,4-dichloro butane.

precursor to synthesize mixed oxide base catalysts finding applications in various base catalyzed organic transformations such as aldol condensation, Knoevenagel condensation, Claisen-Schmidt condensation, Isomerization, Michael addition, Aza-Michael addition reactions, *etc*. for the synthesis of fine chemicals.[10,15-32] Hydrotalcite can be an appropriate alternative of conventional homogeneous base catalysts (like aqueous $K_2CO_3$) for *N*-heterocyclization/di *N*-alkylation of primary amines with di-halo alkanes to synthesize *N*-substituted azacycloalkanes. To the best of our knowledge, there is no report on application of solid base catalysts for *N*-heterocyclization/di *N*-alkylation of amines. Here, we report a simple, solvent free and catalytic one-pot approach for selective synthesis of *N*-substituted azacyclopentanes (one of *N*-substituted azacycloalkanes) by di *N*-alkylation with a di-halo alkane (1,4-dichloro butane) as dialkylating agent using hydrotalcite (Mg-Al hydrotalcite) as solid base catalyst (Scheme 2). The primary amines having different types of substituents such as aromatic, benzylic, alicyclic and alkyl on the amino group were used to demonstrate the efficiency of hydrotalcite for di N-alkylation reaction.

Several homogeneous and heterogeneous base catalysts have been reported for *N*-alkylation (mono *N*-alkylation and di *N*-alkylation) reactions of amines for the synthesis of secondary and tertiary amines.[33] The reported methods have several draw backs like use of high amount of catalysts, hazardous nature of catalysts, requirement of solvent, long reaction duration, formation of side products (poor selectivity of desired product), post reaction work up, generation of inorganic waste, *etc.* The present study demonstrates that hydrotalcite could also be a potential solid base catalyst for mono *N*-alkylation and di *N*-alkylation reactions overcoming the above problems.

## Experimental

**Materials.** Magnesium nitrate ($Mg(NO_3)_2{\cdot}6H_2O$), aluminium nitrate ($Al(NO_3)_3{\cdot}9H_2O$), sodium carbonate, sodium hydroxide, methanol, aniline, benzyl amine, cyclohexyl amine and *n*-butyl amine were procured from s.d. Fine Chemicals, India, and 1,4-dichloro butane from Merck, Germany.

**Catalyst Synthesis and Characterization.** The Mg-Al hydrotalcite (HT) samples with Mg/Al molar ratios of 2.0, 2.5, 3.0 and 3.5 denoted as HT-2, HT-2.5, HT-3 and HT-3.5 were synthesized by co-precipitation method.[10] The aqueous solution of $Mg(NO_3)_2{\cdot}6H_2O$ and $Al(NO_3)_3{\cdot}9H_2O$ (0.088 mol) was prepared by dissolving 0.176, 0.22, 0.264 and 0.308 mol of $Mg(NO_3)_2{\cdot}6H_2O$ separately in 200 mL distilled water to synthesize HT-2, HT-2.5, HT-3 and HT-3.5 respectively. The prepared aqueous solution of $Mg(NO_3)_2{\cdot}6H_2O$ and $Al(NO_3)_3{\cdot}9H_2O$ was added drop wise into an aqueous solution of NaOH (0.72 mol) and $Na_2CO_3$ (0.21 mol) dissolved in 200 mL distilled water under stirring at room temperature. The mixture was transferred into a Teflon coated stainless steel autoclave and aged at 70 ºC for 14 h. The precipitates were filtered, washed with hot distilled water until pH of the filtrate was 7 and then dried in an oven at 80 ºC for 14 h. The hydrotalcite samples were calcined at 450 °C for 2 h to prepare the activated hydrotalcite samples (AHT-2, AHT-2.5, AHT-3 and AHT-3.5).

The synthesized hydrotalcite (HT) samples were characterized by Powder X-ray diffraction (XRD) using (Philips X'pert, using CuK$\alpha$ radiation: $\lambda$ = 1.5405 Å, in $2\theta$ range of 2-70º) and Fourier transform infrared (FT-IR) spectroscopy (IRPrestige-21, Shimadzu, using a Diffuse Reflectance Scanning disc technique, mixing the sample with dried KBr (4 wt % sample in KBr), in the wavelength range of 400-4000 $cm^{-1}$). Thermo gravimetric analysis (TGA) of hydrotalcite samples were carried out using Mettler thermal analyzer, TGA/DSC 1 SF/752, by heating the sample in the range of 50-900 ºC with a heating rate of 10 ºC $min^{-1}$ under nitrogen flow (50 mL $min^{-1}$). The BET surface area (activated at 110 ºC for 2 h under vacuum) was determined from $N_2$ adsorption data (by using BET equation) measured at 77 K using Quantachrome NOVA 1000e surface area analyzer.

**General Procedure for HT Catalyzed di *N*-Alkylation of Primary Amines with 1,4-Dichloro Butane to Synthesize *N*-Substituted Azacyclopentanes.** A mixture of primary amine (**1**) and 1,4-dichloro butane (**2**) in required molar ratio was taken in a 50 mL reaction tube of reaction station (12 Place Heated Carousel Reaction Station, RR99030, Radleys Discovery Technologies, UK) along with the pre-activated (at 100 °C for 2 h) HT catalyst (Scheme 2). The reaction was carried out at desired temperature under purging of $N_2$ gas and stirring for required reaction time. The HCl gas evolved during the reaction was removed from the reactor with the flow of $N_2$ through a glass tube connected at the top of condenser and was scrubbed in the water. After completion of reaction, the reaction mixture was cooled and diluted with dichloromethane (5 mL) and washed with distilled water (10 mL). The catalyst remained suspended in aqueous layer, which could be filtered to recover it from the aqueous phase. The organic layer was analysed with gas chromatograph (Sigma Instruments, India) having a HP-5 (30 meter) capillary column with a programmed oven temperature from 50 to 250 ºC, a 0.5 mL $min^{-1}$ flow rate of $N_2$ as carrier gas and FID detector. The conversion of 1,4-dichloro butane (dialkylating agent) was calculated on the basis of its weight per cent.

The products were characterized by gas chromatography mass spectrometry (GC-MS) using gas chromatograph mass spectrometer (Agilent 5975 GC/MSD with 7890A GC system) having HP-5 capillary column of 60 m length and 250 µm diameter with a programmed oven temperature from 50 to 250 ºC, at 1 mL $min^{-1}$ flow rate of He as carrier gas and ion source at 230 ºC.

## Results and Discussion

**Characterization of Synthesized Hydrotalcite Catalysts.** XRD patterns of synthesized hydrotalcite samples (Fig. 1(a)) showed intense symmetric peaks in the range of 10° to 25° $2\theta$ and broad asymmetric peaks in 30° to 50° $2\theta$ range showing highly crystalline layered structure of the material.[10]

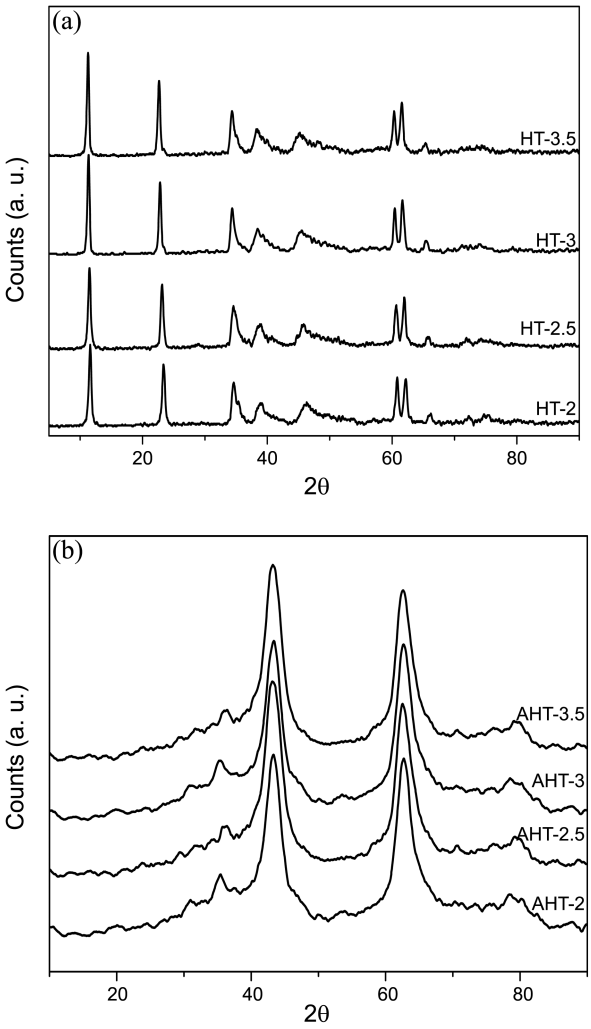



**Figure 1.** XRD patterns of (a) synthesized and (b) calcined hydrotalcite samples.

**Table 1.** Crystallinity and BET surface area of hydrotalcite samples

| S. No. | Catalyst | *d*-spacing (003 plane) | BET Surface area ($m^2/g$) |
|---|---|---|---|
| 1 | HT-2 | 7.60 | 60 |
| 2 | HT-2.5 | 7.68 | 64 |
| 3 | HT-3 | 7.78 | 68 |
| 4 | HT-3.5 | 7.84 | 70 |

The basal spacing of 003 plane ($d_{003}$ = 7.60 Å) indicates the presence of $CO_3^{2-}$ anions in interlayer space of hydrotalcite samples. The *d* spacing of 003 plane was found to be increasing with increasing Mg/Al molar ratio of hydrotalcite samples (Table 1) showing the decrease in the crystallinity of the samples. The similar observations were also reported in the literature.[34] The calcination of hydrotalcite samples at 450 °C resulted to Mg-Al mixed oxide [Mg(Al)O] phase showing broad peaks in XRD of calcined hydrotalcite samples (Fig. 1(b)).

FT-IR spectra of synthesized hydrotalcite samples (Fig. 2) possess a broad band at 3100-3776 $cm^{-1}$, which is attributed to the stretching vibrations of structural -OH groups of the

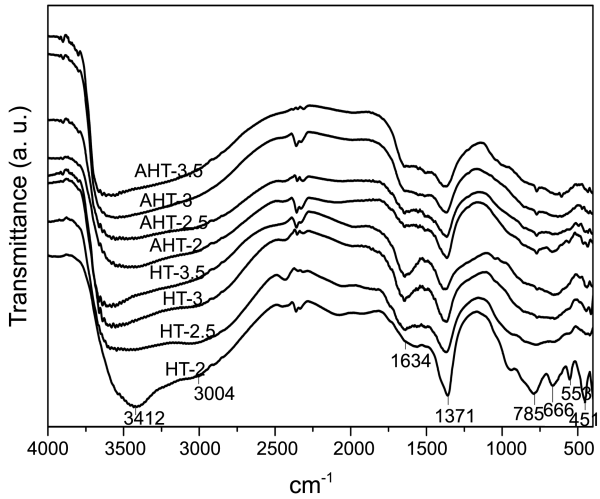



**Figure 2.** FTIR spectra of (a) synthesized and (b) calcined hydrotalcite samples.

brucite layer. The bands at 1634 and 1371 $cm^{-1}$ indicates the presence of interlayer $H_2O$ molecules and $CO_3^{2-}$ anions, respectively. A shoulder at ~3000 $cm^{-1}$ reveals the presence of hydrogen bonding between $H_2O$ molecules and interlayer $CO_3^{2-}$ anions. The band at 553 $cm^{-1}$ is assigned to the translation mode of -OH groups mainly influenced by the aluminium and magnesium cations.[35] FTIR spectra of calcined hydrotalcite samples (Fig. 2) show disappearance of the band at 1634 $cm^{-1}$ and ~3000 $cm^{-1}$ and reduced intensity of the band at 3100-3776 $cm^{-1}$ and 1370 $cm^{-1}$ indicating the removal of interlayer water molecules and $CO_3^{2-}$ anions on calcination.

In the thermogravimetric analysis (TGA) of hydrotalcite sample (HT-2) (Fig. 3), two steps weight loss was observed. The first step weight loss in the temperature range of about 50 to 250 °C comprises the loss of physically adsorbed water molecules, interlayer water molecules and dehydroxylation of layer. The second step weight loss in the temperature range of about 270 to 600 °C was attributed to complete dehydroxylation of layers and removal of interlayer $CO_3^{2-}$

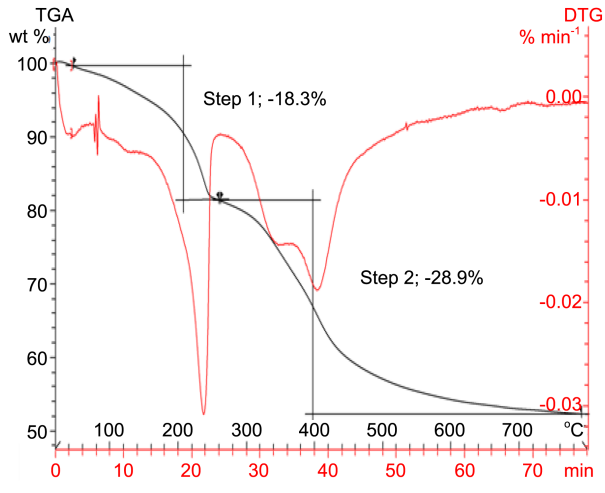



**Figure 3.** TGA-DTG profile of hydrotalcite sample (HT-2).

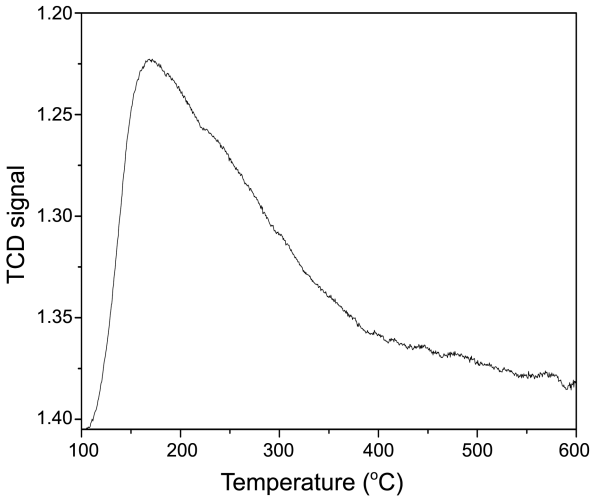


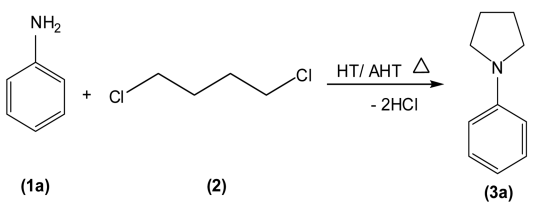

**Figure 4.** $CO_2$-TPD profile of hydrotalcite sample (HT-2).

anions collapsing the layered structure of hydrotalcite. The TGA profiles of other hydrotalcite samples (HT-2.5, HT-3 and HT-3.5) were similar to that of HT-2 sample.

The $CO_2$-TPD profile of hydrotalcite sample (HT-2) indicates adsorption of significant amount of $CO_2$ showing the presence of considerable amount of basicity in the hydrotalcite (Fig. 4). The $CO_2$-TPD profile of hydrotalcite is showing predominantly the peak maxima (maximum $CO_2$ desorption rate) at ~169 °C revealing the presence of significantly medium strength basic sites in the sample.[36]

The BET surface area of HT-2, HT-2.5, HT-3 and HT-3.5 samples, measured by $N_2$ adsorption desorption study at 77 K, was 60, 64, 68 and 70 $m^2/g$ respectively (Table 1) leading to the conclusion that these samples did not show much textural changes.

**Synthesis of *N*-Substituted Azacyclopentane by HT Catalyzed di *N*-Alkylation of Primary Amines with 1,4-Dichloro Butane.** The hydrotalcite (HT) samples with different Mg/Al molar ratio (HT-2, HT-2.5, HT-3 and HT-3.5) were first used for di *N*-alkylation reaction of aniline (**1a**) with 1,4-dichloro butane (**2**) to synthesize *N*-phenyl azacyclopentane (**3a**) in order to screen the best catalyst for the synthesis (Scheme 3). In addition, the calcined hydrotalcite (AHT) samples (AHT-2, AHT-2.5, AHT-3 and AHT-3.5) were also tested for di N-alkylation reaction of aniline to assess the catalytic activity of Mg/Al mixed oxide for this reaction. The reaction was also carried out without catalyst at 180 °C for 2 h, but no product formation was observed indicating that the reaction is catalytic.




**Scheme 3.** Synthesis of *N*-phenyl azacyclopentane by hydrotalcite catalyzed di *N*-alkylation of aniline with 1,4-dichloro butane.

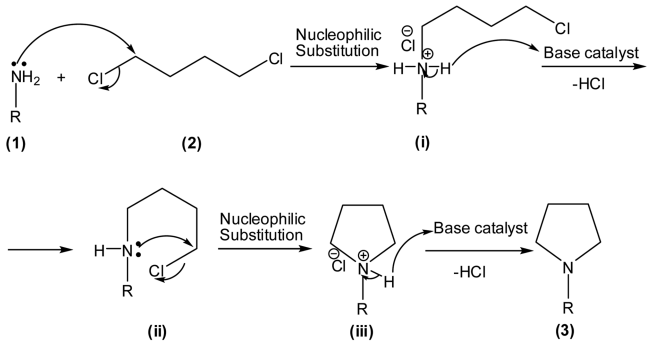
**Table 2.** Conversion of 1,4-dichloro butane and selectivity of *N*-phenyl azacyclopentane in di *N*-alkylation of aniline using different hydrotalcite samples[a]

| S. No. | Samples[b] | Conversion (wt %) of 1,4-dichloro butane | Selectivity (wt %) of *N*-phenyl azacyclopentane |
|---|---|---|---|
| 1 | HT-2 | 52 | 99 |
| 2 | AHT-2 | 41 | 99 |
| 3 | HT-2.5 | 49 | 99 |
| 4 | AHT-2.5 | 43 | 99 |
| 5 | HT-3 | 48 | 99 |
| 6 | AHT-3 | 43 | 99 |
| 7 | HT-3.5 | 50 | 99 |
| 8 | AHT-3.5 | 42 | 99 |

[a]Reaction condition: 0.01 mmol aniline, 0.01 mmol 1,4-dichloro butane, 0.1 g catalyst, reaction temperature = 180 ºC, reaction time = 2 h. [b]HT-2, HT-2.5, HT-3 and HT-3.5 are as synthesized hydrotalcite samples with Mg/Al molar ratios of 2.0, 2.5, 3.0 and 3.5 and AHT-2, AHT-2.5, AHT-3 and AHT-3.5 are respective calcined (450 °C for 2 h) hydrotalcite samples.

The as synthesized as well as calcined hydrotalcite samples were observed to be having significant activity for di *N*-alkylation of aniline with 1,4-dichloro butane. However, as synthesized hydrotalcite samples gave slightly higher conversion of 1,4-dichloro butane (48 to 52%) as compared to the calcined hydrotalcite samples (41 to 43% conversion of 1,4-dichloro butane) (Table 2). It indicates that as synthesized hydrotalcite samples are highly active solid base catalysts for base catalyzed di *N*-alkylation reaction of aniline with 1,4-dichloro butane. The selectivity of *N*-phenyl azacyclopentane was ~99% with both as synthesized as well as calcined hydrotalcite samples. The as synthesized hydrotalcite possesses mainly Brønsted basic sites (because of hydroxide ions), whereas, the calcined hydrotalcite possesses predominantly strong Lewis (because of isolated $O^{2-}$ anions) sites with few weak Brønsted basic sites.[34] The Brønsted sites of hydrotalcite seems to be more efficient to catalyze this reaction as compared to Lewis sites giving higher conversion of 1,4-dichloro butane with as synthesized hydrotalcite than calcined hydrotalcite. With increasing Mg/Al molar ratio, the basicity of as synthesized as well as calcined hydrotalcites increases.[29] However, we did not notice any remarkable change in activity of hydrotalcites (in terms of 1,4-dichloro butane conversion) for di *N*-alkylation of aniline on variation of Mg/Al molar ratio from 2 to 3.5. As the synthesized hydrotalcite without calcination gave highest conversion of 1,4-dichloro butane as compared to calcined catalyst, one of the hydrotalcites, HT-2 was selected for the detail study on base catalyzed di *N*-alkylation reaction of amines with 1,4-dichloro butane.

The plausible mechanistic pathway for the base catalyzed di *N*-alkylation of primary amine with 1,4-dichloro butane to *N*-substituted azacyclopentane, which is reported in the literature,[8] is given in Scheme 4, which involves the formation of quaternary ammonium salts (**i** and **iii**) and mono *N*-alkylated or secondary amine (**ii**) as intermediates. The




**Scheme 4.** Plausible mechanistic pathway of base catalyzed di *N*-alkylation of primary amine with 1,4-dichloro butane to *N*-substituted azacyclopentane [8].

primary amine (**1**) acts as a nucleophile, which does nucleophilic substitution of chloro group of 1,4-dichloro butane (**2**) and form a quaternary ammonium salt (**i**). The catalyst (base) participation is required for the removal of proton from quaternary ammonium ion (**i**) to give mono *N*-alkylated (secondary amine) intermediate product (**ii**) and HCl as by-product. The secondary amine (**ii**) undergoes cyclization by nucleophilic substitution of chloro group of the chain by secondary amino group resulting into a five membered cyclic quaternary ammonium salt (**iii**). The base catalyzed removal of proton from cyclic quaternary ammonium ion gives *N*-substituted azacyclopentane (**3**).

The optimization of the reaction parameters such temperature, molar ratio of substrates, catalyst loading, solvent effect etc. were carried out to study their effect on catalytic performance of hydrotalcite for di *N*-alkylation reaction and to achieve highest conversion of 1,4-dichloro butane to the product. The reaction temperature was observed to be affecting the conversion of 1,4-dichloro butane in hydrotalcite catalyzed di *N*-alkylation reaction of aniline with 1,4-dichloro butane to *N*-phenyl azacyclopentanes (Fig. 5). With increasing the reaction temperature from 100 °C to 180 °C, the conversion of 1,4-chloro butane significantly increased giving highest conversion (50%) and selectivity of *N*-phenyl azacyclopentane (~99%) at 180 °C. Further increase in reaction temperature (at 200 °C) lowered the conversion of 1,4-dichloro butane (40%). The less conversion of 1,4-dichloro butane at 200 °C may be due to high reaction temperature, at which 1,4-dichloro butane (boiling point: 161 °C) will be mostly in vapour phase reducing its concentration in reaction mixture for the reaction with aniline (boiling point: 184 °C). The reaction temperature did not affect the selectivity of N-phenyl azacyclopentane giving similar selectivity of the product (~99%) from 100 °C to 200 °C (Fig. 5). As the highest conversion of 1,4-dichloro butane was observed at 180 °C, therefore 180 °C temperature was found as optimum reaction temperature to achieve highest conversion of 1,4-dichloro butane to *N*-phenyl azacyclopentane.

The molar ratio of aniline and 1,4-dichloro butane was found to be an important reaction parameter affecting the conversion of 1,4-dichloro butane. With varying aniline to

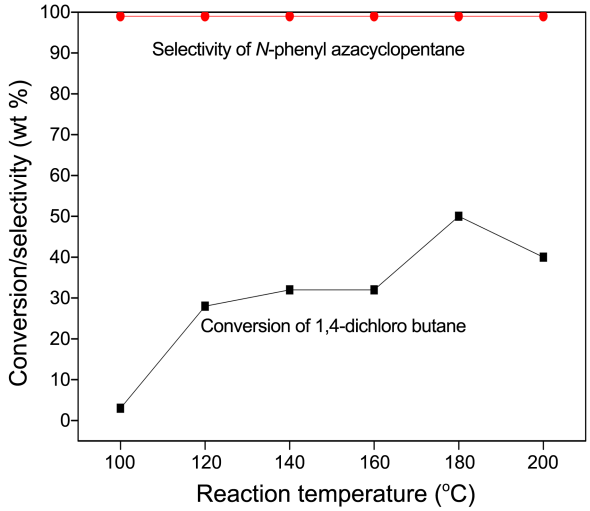
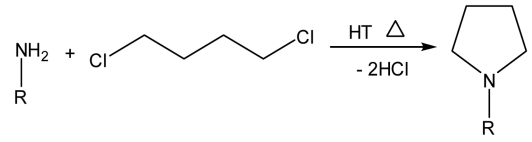



**Figure 5.** Variation of conversion of 1,4-dichloro butane and selectivity of *N*-phenyl azacyclopentane with reaction temperatures in hydrotalcite catalyzed di *N*-alkylation of aniline [Reaction condition: 0.01 mmol aniline, 0.01 mmol 1,4-dichloro butane, 0.1 g catalyst, reaction time = 2 h.].

1,4-dichloro butane molar ratio from 1:1 to 2:1, the conversion of 1,4-dichloro butane was significantly increased from 50% to 98%. At aniline to 1,4-dichloro butane molar ratio of 2, the concentration of aniline (nucleophile) is more in the reaction mixture, which enhances the probability of 1,4-dichloro butane molecule to be reacted with aniline molecules for nucleophilic substitution. When aniline was in equimolar quantity (molar ratio of 1:1) or in less molar quantity (molar ratio of 1:2), the conversion of 1,4-dichloro butane was found to be decreased to 50% and 30% respectively. This may be attributed to availability of comparatively less number of aniline molecules (nucleophiles) for nucleophilic substitution reaction of 1,4-dichloro butane molecules. However, the substrates molar ratio did not affect the selectivity of *N*-phenyl azacyclopentane.

The kinetic study of hydrotalcite catalyzed di *N*-alkylation of aniline with 1,4-dichloro butane to *N*-phenyl azacyclopentane, at optimized reaction temperature and molar ratio of substrate, revealed that the reaction is very fast giving 96% conversion of 1,4-dichloro butane and ~99% selectivity of *N*-phenyl azacyclopentane within 30 min. There was no significant change in conversion or selectivity after 30 min. of the reaction, which shows that 30 min. is the optimum reaction duration giving highest conversion of 1,4-dichloro butane to *N*-phenyl azacyclopentane.

The optimum catalyst amount required to achieve highest conversion of 1,4-dichloro butane in di *N*-alkylation of aniline was estimated by varying the substrate (1,4-dichloro butane) to catalyst weight ratio from 3 to 40. The conversion was observed to be highest at substrate/catalyst weight ratio of 6 (95%), which remained almost steady upto substrate/catalyst wt. ratio of 20 and decreased to 75% at very less catalyst loading (substrate/catalyst weight ratio of 40). It clearly indicates that hydrotalcite is highly active for di *N*-alkylation reaction and it can be used in very small catalytic




**(1a-d)** **(2)** **(3a-d)**

**(1a)** *R* = Phenyl; aniline **(3a)** *N*-phenyl azacyclopentane,
**(1b)** *R* = Benzyl; benzyl amine **(3b)** *N*-benzyl azacyclopentane
**(1c)** *R* = Cyclohexyl; cyclohexyl amine **(3c)** *N*-cyclohexyl azacyclopentane
**(1d)** *R* = *n*-butyl; *n*-butyl amine **(3d)** *N*-*n*-butyl azacyclopentane.

**Scheme 5.** Synthesis of *N*-substituted azacyclopentanes by hydrotalcite catalyzed di *N*-alkylation of primary amines with 1,4-dichloro butane.

amount for the synthesis.

From the study, it is evident that hydrotalcite can be a potential solid base catalyst for di *N*-alkylation of amines to synthesize *N*-substituted azacyclopentanes. The use of hydrotalcite for di *N*-alkylation of primary amines with 1,4-dichloro butane was explored for the synthesis of *N*-substituted azacyclopentanes (**3a-d**) using four different types of primary amines such as aromatic, benzylic, alicyclic and alkyl substituted amines (**1a-d**) under optimized reaction conditions (Scheme 5).

The hydrotalcite was found to be efficient catalyst for di *N*-alkylation of all four types of substrates (aniline, benzyl amine, cyclohexyl amine and *n*-butyl amine) giving 82 to 96% conversion and ~99% selectivity of respective azacyclopentanes (Table 3). The GC-MS data of *N*-substituted azacyclopentanes (**3a-d**) are as follows: *N*-phenyl azacyclopentane (**3a**): *m*/*z* 146, 130, 119, 104, 91, 77, 65; *N*-benzyl azacyclopentane (**3b**): *m*/*z* 160, 132, 91, 84, 77, 70, 65; *N*-cyclohexyl azacyclopentane (**3c**): *m*/*z* 127, 84, 70, 55; *N*-*n*-butyl azacyclopentane (**3d**): *m*/*z* 153, 149, 110, 97, 84, 67, 55.

It was noticed that the optimum reaction temperature varied for different types of amine substrates (Table 3). The optimum reaction temperature required to achieve highest conversion of 1,4-dichloro butane in di *N*-alkylation of amines was found to be in the range of 160-180 °C (except for *n*-butyl amine). In the reaction of aniline with 1,4-dichloro butane to *N*-phenyl azacyclopentane (**3a**), the highest conversion of 1,4-dichloro butane (96%) was achieved at 180 °C, whereas with benzyl amine and cyclohexyl amine, the highest conversion of 1,4-dichloro butane (94%) was obtained at 160 °C (Table 3). The lower reaction temperature for the reaction with benzyl amine and cyclohexyl amine may be because of their higher reactivity for di N-alkylation reaction than the reactivity of aniline. The possible reason for the lower reactivity of aniline than benzyl amine and cyclohexyl amine is its comparatively poor nucleophilicity. This is due to the conjugation of lone pair of electron of amino group with aromatic ring in aniline, which decreases the availability of lone pair of electron on amino group for nucleophilic substitution reaction with 1,4-dichloro butane (Scheme 4). Whereas in benzyl amine and cyclohexyl amine, the availability of lone pair of electrons on amino group will be more for the substitution reaction and therefore, benzyl amine and cyclohexyl amine are more reactive. The less conversion of 1,4-dichloro butane with *n*-butyl amine (82% at 80 °C) may be because of low boiling point of *n*-butyl amine (79 °C) than the optimum reaction temperature required to achieve highest conversion. In di *N*-alkylation of all amines with 1,4-dihydroxy butane as dialkylating agent under optimized reaction condition, no product formation was observed even after 2 h (Table 3). The most probable reason for no reaction of 1,4-dihydroxy butane with amines can be attributed to less or no reactivity of 1,4-dihydroxy butane for nucleophilic substitution reaction with amine due to presence of a poor leaving -OH group. The 1,4-dichloro butane having -Cl groups, a good leaving group, is comparatively more reactive for nucleophilic substitution reactions, which can be easily replaced by a nucleophile *i.e.*, amino compounds to form quaternary

**Table 3.** Conversion of 1,4-dichloro butane and selectivity of *N*-substituted azacyclopentane in hydrotalcite catalyzed di *N*-alkylation of primary amines[a]

| Amines | React[n] temp. (ºC) | 1,4-dichloro butane Conversion (wt %) | *N*-substituted azacyclopentane Selectivity (wt %) |
|---|---|---|---|
| $C_6H_5$-$NH_2$ (**1a**) | 100 | 64 | 99 |
| | 120 | 68 | 99 |
| | 140 | 76 | 99 |
| | 160 | 89 | 99 |
| | 180 | 96 | 99 |
| | 180 | 90[b] | 99 |
| | 180 | 85[c] | 99 |
| | 200 | 94 | 99 |
| $C_6H_5$-$CH_2$-$NH_2$ (**1b**) | 100 | 59 | 99 |
| | 120 | 75 | 99 |
| | 140 | 89 | 99 |
| | 160 | 94 | 99 |
| | 180 | 93 | 99 |
| $C_6H_{11}$-$NH_2$ (**1c**) | 100 | 57 | 99 |
| | 120 | 60 | 99 |
| | 140 | 70 | 99 |
| | 160 | 94 | 99 |
| | 180 | 94 | 99 |
| $C_4H_9$-$NH_2$ (**1d**) | 80 | 82 | 99 |
| | 100 | 78 | 99 |
| Di *N*-alkylation of primary amines with 1,4-dihydroxy butane using hydrotalcite.[d] | | | |
| $C_6H_5$-$NH_2$ (**1a**) | 180 | No product formation | |
| $C_6H_5$-$CH_2$-$NH_2$ (**1b**) | 180 | No product formation | |
| $C_6H_{11}$-$NH_2$ (**1c**) | 180 | No product formation | |
| $C_4H_9$-$NH_2$ (**1d**) | 100 | No product formation | |

[a]0.02 mmol aniline, 0.01 mmol 1,4-dichloro butane, 0.1 g catalyst, reaction time = 30 min. [b]Reaction in presence of nitrobenzene (as polar solvent). [c]Reaction in presence of *n*-hexadecane (as non-polar solvent). [d]0.02 mmol aniline, 0.01 mmol 1,4-dihydroxy butane, 0.1 g catalyst, reaction time = 2 h.

ammonium salt (Scheme 4).

The reaction was also carried out at optimized reaction condition in polar (nitrobenzene) and non polar solvents (*n*-hexadecane) to study the effect of solvent nature on the performance of hydrotalcite catalyst. It was observed that the conversion was reduced to 85-90% in presence of solvents (polar and non polar) in comparison of the solvent free condition (Table 3), which shows that catalyst is more active in solvent free medium.

The proposed route for di *N*-alkylation of primary amines with 1,4-dichloro butane is selective for *N*-heterocyclization of amines to synthesize of *N*-substituted azacyclopentanes. The synthesis selectively (> 99%) results to *N*-substituted azacyclopentane (**3a-d**). We did not observed the formation of any side products, which are possible to be formed by the side reaction like mono *N*-alkylation of amine with 1,4-dichloro butane, di *N*-alkylation of amine with two different molecules of 1,4-dichloro butane and *N*-alkylation of two molecules of amines with one molecule of 1,4-dichloro butane, *etc*.

Several *N*-substituted azacycloalkanes were synthesized in good yield by di *N*-alkylation of primary amines with di-halo alkanes using $K_2CO_3$ as base catalyst under microwave irradiation in aqueous medium.[8] However, the reported synthesis is carried out in homogeneous condition using equimolar amount of homogeneous base catalyst ($K_2CO_3$), which requires post reaction work up to separate the catalyst from reaction mixture generating alkaline waste. Furthermore, the microwave assisted synthesis, which is very difficult to handle at large scale for industrial production, the highest yield of the product could be achieved after 20 min. of microwave irradiation. It should be noted that using catalytic amount of hydrotalcite under solvent free condition and by thermal heating, the proposed synthesis route yields the comparable amount of the product within 30 min. without generating any by-product.

To regenerate the spent hydrotalcite catalyst (HT-2), the spent catalyst was washed with acetone followed by drying at 100 °C for 2 h. The catalytic activity of regenerated catalyst was checked for the synthesis of *N*-phenyl azacyclopentane (**3a**), which showed almost similar activity (92-96% conversion of 1,4-dichloro butane with ~99% selectivity of *N*-phenyl azacyclopentane) in three reaction cycles as fresh catalyst (Table 4). The spent catalyst after third cycle was characterized by FTIR analysis, which did not show any chemical change in the catalyst as FTIR spectrum of the spent catalyst resembles that of fresh catalyst (Fig. 6). It indicates that hydrotalcite is not affected by the HCl produced during reaction and is chemically stable in this reaction.

**Table 4.** Regeneration study of spent HT-2 catalyst[a]

| Reaction cycle | Conversion (wt %) of 1,4-dichloro butane | Selectivity (wt %) of *N*-phenyl azacyclopentane |
|---|---|---|
| Fresh catalyst | 96 | 99 |
| I | 96 | 99 |
| II | 94 | 99 |
| III | 92 | 99 |

[a]Reaction condition: 0.02 mmol aniline, 0.01 mmol 1,4-dichloro butane, 0.1 g catalyst, reaction temperature = 180 ºC, reaction time = 30 min.

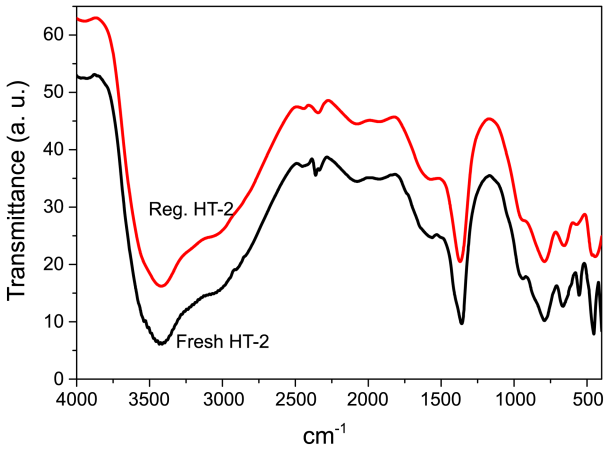



**Figure 6.** FTIR spectra of fresh and regenerated (after 3rd cycle) HT-2 catalysts.

## Conclusions

Hydrotalcite was found to be a potential solid base catalyst for di *N*-alkylation reaction (*N*-heterocyclization) of primary amines with 1,4-dichloro butane to synthesize *N*-substituted azacyclopentanes under solvent free condition. The proposed route is an economically viable and environmentally benign method for the synthesis of *N*-substituted azacyclopentanes using catalytic amount of hydrotalcite solid base catalyst. The reaction conditions and the nature of substituent present in amine were observed to affect the conversion of 1,4-dichloro butane to *N*-substituted azacyclopentanes. The 1,4-dichloro butane was found to be an appropriate dialkylating agent for base catalyzed *N*-heterocyclization of primary amine to synthesize nitrogen containing heterocyclics. The hydrotalcite is chemically stable in the reaction and is easily regenerated and reused with retention of catalytic activity. The catalytic application of hydrotalcite can also be explored for various mono *N*-alkylation reactions to synthesize secondary and tertiary amines from primary and secondary amines respectively.

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