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# A novel *N*-alkylation of amines by alkyl halides on mixed oxides at room temperature

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## Abstract

Selective liquid phase *N*-alkylation of amines by alkyl halides using  $\text{Al}_2\text{O}_3\text{--OK}$  as a catalyst in the presence of acetonitrile at room temperature (30 °C) is described. The  $\text{Al}_2\text{O}_3\text{--OK}$  catalyst was characterized by XRD, SEM–EDXS, elemental analysis, particle size analysis, BET surface area, pore size and average pore diameter. The catalyst used for this synthetically useful transformation showed a considerable level of reusability as well as good activity.

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*Keywords:* *N*-Alkylation; Mixed oxides; Tertiary amines; Liquid phase reaction; Room temperature (30 °C)

## 1. Introduction

The development of simple, efficient and highly selective methods for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. The reactions of amines have been a topic of immense research interest due to their synthetic utility [1] and biological activity [2]. Among these, C–N bond formation is one of the most important transformations in organic synthesis. Amines are widely used as intermediates to prepare solvents, fine chemicals, agrochemicals, pharmaceuticals and catalyst for polymerization [3].

The nucleophilic attack of alkyl halides by primary and secondary amines is useful for the preparation of tertiary amines but the reactions are invariably slow and give rise to a mixture of secondary and tertiary amines [4]. Thermal reaction between alkyl halides and amines in the presence of a base requires longer reaction time period and affords lower yields of desired product [5,6]. Although the rela-

tively similar Ullman and Goldberg reactions with copper catalysts [7,8] and the Pd catalyzed Buchwald–Hartwig reaction have been studied in detail [9,10] transition metal-free amination of electron rich benzylic halides has been largely unexplored [11]. The alkylation of amines has also been accomplished by the reaction of an alkylating reagent and an amine in the presence of base like sodium hydride or potassium carbonate [12,13]. *N*-Alkylation of carbamates was reported using cesium carbonate in presence of a phase transfer catalyst [14]. The *N*-alkylation can be also accomplished by bases like  $\text{CsOH} \cdot \text{H}_2\text{O}$ ,  $\text{CsCO}_3$  and various ionic liquids [15–19]. Recently Varma et al. and his coworker studied the direct generation of tertiary amines under microwave irradiation, but recycling of this catalyst was hampered by the homogeneous medium of the catalyst [20].

However, some of these methods are limited by harsh reaction conditions, low yields, long reaction time and use of toxic solvents or catalysts and many of which do not show recyclability. Therefore, the development of mild, efficient, environmentally more benign method of *N*-alkylation of heterocyclic compounds which bear an acidic hydrogen atom attached to nitrogen is still a major challenge in organic synthesis.

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We recently reported several transition metals based mesoporous silicates, aluminophosphate molecular sieves and mixed oxides, as catalysts for a variety of industrially important organic reactions as possible alternatives to standard synthesis of a wide variety of precursors and intermediates. Reactions like reduction of aromatic nitro and carbonyl functions and alkylation have been successfully carried out with these metal oxides [21–26].

In continuation of our earlier work, we report herein an efficient method for the synthesis of tertiary amines via *N*-alkylation of amines by alkyl halides in liquid phase using acetonitrile on reusable  $\text{Al}_2\text{O}_3\text{-OK}$  catalyst at room temperature (30 °C).

## 2. Experimental

### 2.1. Catalyst preparation

The preparation of  $\text{Al}_2\text{O}_3\text{-OK}$  was carried out in the same manner as described in the previous report [27,28]. 26 g  $\text{KNO}_3$  and 74 g  $\text{Al}_2\text{O}_3$  were crushed in mortar, and then appropriate deionised water was added which can be absorbed by  $\text{Al}_2\text{O}_3$ . After grinding, the mixture was dried at 110 °C for 1 h, and then activated at 600 °C for 3 h. When the loading of  $\text{KNO}_3$  is above the threshold, only about 7% of  $\text{KNO}_3$  can be dispersed through the interaction with  $\text{Al}_2\text{O}_3$  support and decomposed in a mild pre-treatment such as evacuation at room temperature, while a lot of undispersed  $\text{KNO}_3$  located in the pores of  $\text{Al}_2\text{O}_3$  forms a new phase such  $\text{K}_2[\text{Al}(\text{NO}_3)]_5$ . Both the residual  $\text{KNO}_3$  and  $\text{K}_2[\text{Al}(\text{NO}_3)]_5$  decomposed during evacuation at 600 °C and potassium ion migrate from the inner to the external surface of  $\text{Al}_2\text{O}_3$  during evacuation process. Consequently, several layers of basic materials such as  $\text{K}_2\text{O}$  overlap on the  $\text{Al}_2\text{O}_3$  result in some basic sites with basic strength  $[\text{H}^-]$  of 27.0.

Table 1  
BET surface area and pore size analysis of  $\text{Al}_2\text{O}_3\text{-OK}$

Catalyst	BET surface area ( $\text{m}^2/\text{g}^{-1}$ )	Pore volume $V_p$ ( $\text{cm}^3/\text{g}^{-1}$ )	Average pore diameter $D_p$ (Å)
$\text{Al}_2\text{O}_3\text{-OK}$	78.56	0.098	51.53

### 2.2. Catalyst characterization

To study the textural characterization of catalyst, surface area measurement and pore size distribution analysis were done, after degassing the sample under high vacuum at 300 °C for 4 h, by nitrogen adsorption on a micromeritics ASAP 2010 instrument at an adsorption temperature of 77 K. (Table 1). The elemental analysis of Al and K was done using a ICP-AES Spectrometer. It was found to be (Al = 27.00%; K = 39.12%). The morphology of catalyst was evaluated by scanning electron microscopy (SEM) and electron dispersive X-ray spectroscopy (EDXS) analysis were done. The particle size of the catalyst was determined on computerized Inspection system (Galai-Cis-1).

### 2.3. X-ray diffraction

The X-ray powder diffraction pattern was obtained using a conventional powder diffractometer (Philips 1050) using graphite monochromatised  $\text{Cu K}\alpha$  radiation operating in Bragg-Brentano ( $\theta/2\theta$ ) geometry. The crystallite size of the catalyst (calcined 600 °C) was found to be 1.40 nm (see Fig. 1).

### 2.4. Particle size analysis

The  $\text{Al}_2\text{O}_3\text{-OK}$  catalyst was ground to # 100 mesh size. The particle size analysis of the  $\text{Al}_2\text{O}_3\text{-OK}$  is shown in

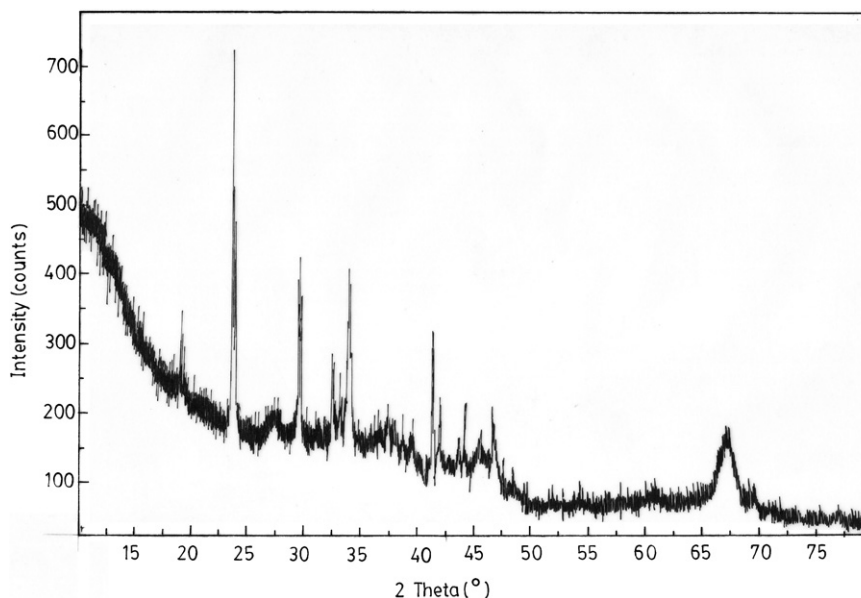


Fig. 1. Catalyst calcined at 600 °C.

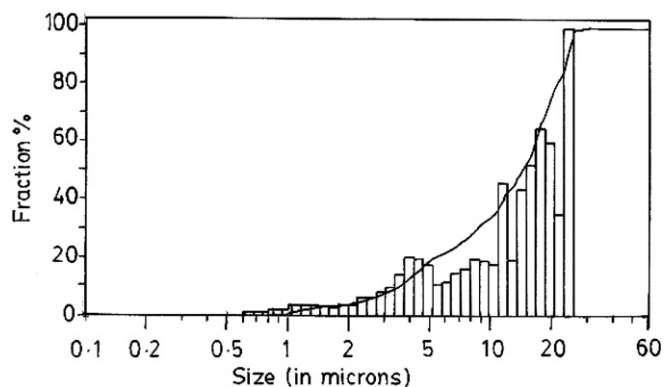


Fig. 2. Particle size of the catalyst  $\text{Al}_2\text{O}_3\text{-OK}$ .

(Fig. 2). The particle size is in the range of 2.10–4.18  $\mu\text{m}$ . The median of the particle size was found to be 14.20  $\mu\text{m}$  and mean was 13.44  $\mu\text{m}$ .

### 2.5. BET surface area and pore size analysis

The  $\text{N}_2$  adsorption–desorption isotherms were measured at 78 K on a Quantachrome Autosorb-I porosimeter. Specific surface area  $S_{\text{BET}}$  were determined with Brunauer–Emmett–Teller (BET) method using adsorption data points in the relative pressure  $P/P_0$ .

Pore volume ( $V_p$ ) and pore diameter ( $D_p$ ) were determined (Table 1).

### 2.6. SEM–EDXS analysis

However, In order to know about the homogeneity of  $\text{Al}_2\text{O}_3\text{-OK}$ , SEM analysis was carried out.

We observed that  $\text{K}_2\text{O}$  base was finely and uniformly distributed on the  $\text{Al}_2\text{O}_3$  support which makes catalyst more active (Fig. 3). The elemental analysis of  $\text{K}_2\text{O}$  on  $\text{Al}_2\text{O}_3$  were obtained by (EDXS) energy dispersive X-ray spectroscopy. See Fig. 4 and Table 2.

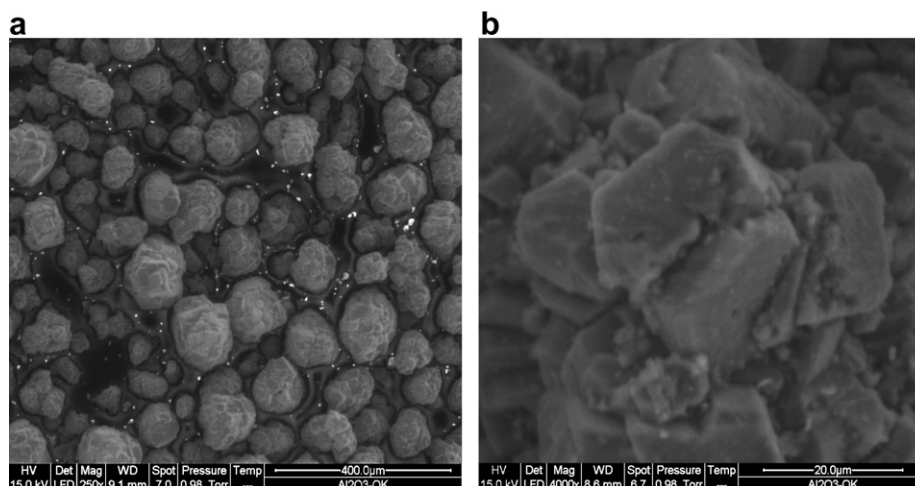


Fig. 3. (a) Scanning electron micrograph of  $\text{Al}_2\text{O}_3\text{-OK}$  at 400  $\mu\text{m}$ . (b) Scanning electron micrograph of  $\text{Al}_2\text{O}_3\text{-OK}$  at 20  $\mu\text{m}$ .

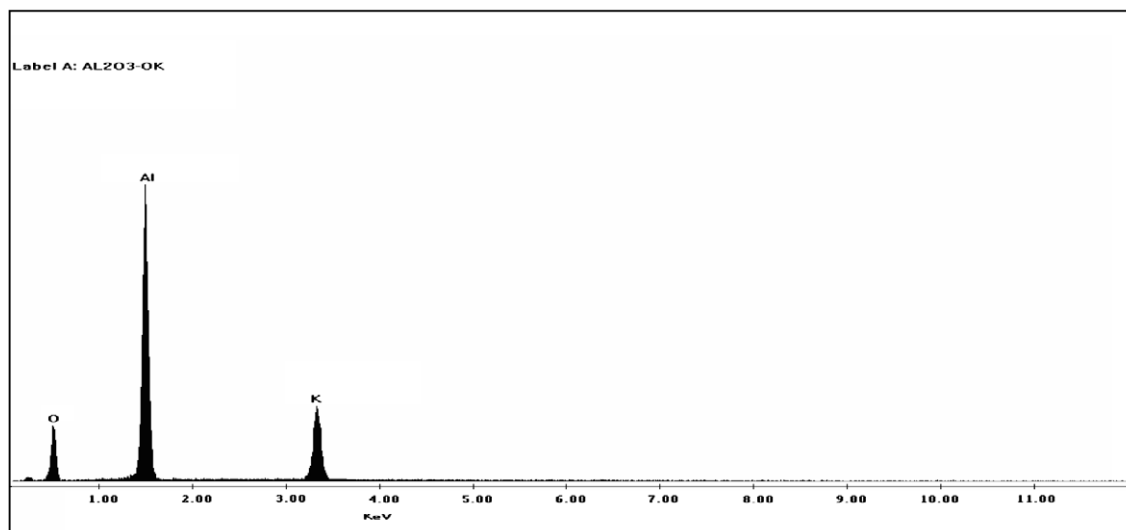
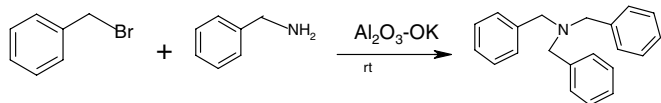


Fig. 4. Electron dispersive X-ray spectrum of  $\text{Al}_2\text{O}_3\text{-OK}$ .

Table 2  
EDXS data of Al<sub>2</sub>O<sub>3</sub>-OK

Element	wt (%)	at. (%)	K-ratio
O K	36.47	51.3	0.0779
Al K	46.96	39.17	0.2979
K K	16.57	9.54	0.1334
Total	100	100	



Scheme 1. Al<sub>2</sub>O<sub>3</sub>-OK catalyzed *N*-alkylation of amines by alkyl halide.

### 2.7. Typical experimental procedure

The liquid phase reaction was carried out in 25 mL round bottom flask equipped with thermometer. In typical *N*-alkylation of amines; amines (10 mmol), halides (10 mmol), acetonitrile (10 mL) and catalyst 20 wt% of amine was added, the stirring was continued for 1–7 h (for reaction conditions, see Table 4). After the reaction was complete (monitored by TLC), the mixture is filtered and the solid is washed with ether (3 × 10 mL). The combined filtrate was treated with 10% NaHCO<sub>3</sub> (10 mL), water (2 × 10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated the solvent to give the product. All the products were confirmed by <sup>1</sup>H NMR, IR and MS techniques.

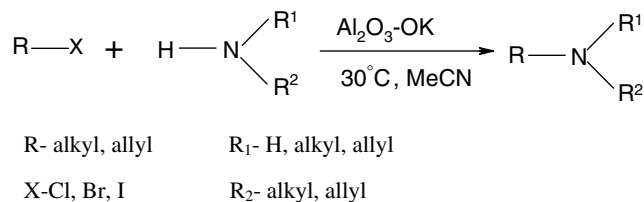
### 3. Results and discussion

In order to develop a convenient reaction protocol for *N*-alkylation of amines, we chose the coupling of benzyl amine and benzyl bromide, as the model reaction (Scheme 1).

*N*-Alkylation of benzyl amines is not possible in the absence of a catalyst. In the catalyst Al<sub>2</sub>O<sub>3</sub>-OK, K<sub>2</sub>O base dispersed on neutral alumina of high surface area. K<sup>+</sup> of K<sub>2</sub>O is the active site for *N*-alkylation. We have carried out different wt% of the catalyst loadings like 5%, 10%, 15% and 20 wt%. Among that Al<sub>2</sub>O<sub>3</sub>-OK gave better yield for 20 wt% of the catalyst. Various solvents also tested for this reaction, we found that acetonitrile is the most effective (85%), nonpolar solvent such as toluene, only modest yield was obtained (32%) the other solvents results are Et<sub>2</sub>O (61%), CHCl<sub>3</sub> (45%), CH<sub>2</sub>Cl<sub>2</sub> (60%), Cl<sub>2</sub>CH<sub>2</sub>Cl<sub>2</sub> (65%). In the absence of acetonitrile, no product could be isolated from the crude reaction mixture; thus solvents play a vital role in this reaction. For the *N*-alkylation of primary amines, the halide: amine ratio (2:1) was used, to avoid the monoalkylated product. (Table 3, entry 4, 6 and 16)

Subsequently, the scope of the reaction of various alkyl halides and amines over Al<sub>2</sub>O<sub>3</sub>-OK was investigated (Scheme 2). Selected results are summarized in Table 4.

The catalyst was also tested for reusability and it was found that it could be reused without loss of activity for five cycles. The reaction of piperidine and 2-phenethyl bromide gave only 20% yield, under solventless conditions, but in acetonitrile the yield was 80% (entry 9, Table 4).



Scheme 2. *N*-Alkylation of primary and secondary amines by alkyl halides.

Table 3  
*N*-Alkylation of amines by alkyl halide at different conditions

Entry	Halide	Amine	Halide:Amine	Products and yields <sup>a</sup>
1			1:1	65% +  15%
2			2:1	85%

Reaction condition : Benzyl amine (10 mmol), benzyl bromide (20 mmol), catalyst (20 wt%) of benzyl amine, acetonitrile (10 mL) at RT (30 °C) for 2 h.

<sup>a</sup> Mono and di products were observed by GC/MS analysis.

Table 4  
Liquid phase *N*-alkylation of amines using alkyl halide at room temperature (30 °C)

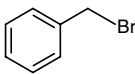

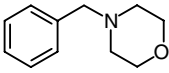
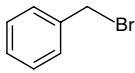

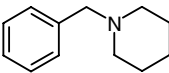
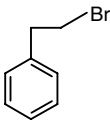

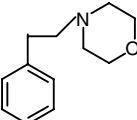
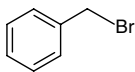
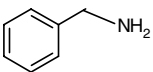
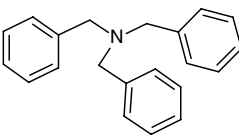

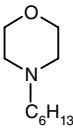
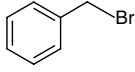
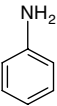
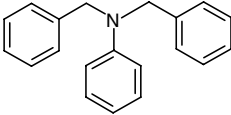

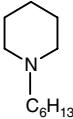
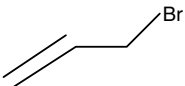
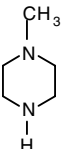
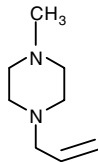
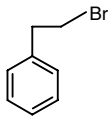

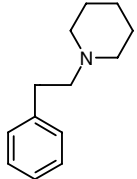

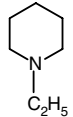
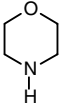
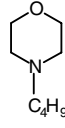
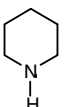
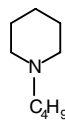
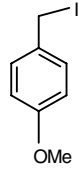
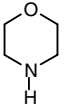
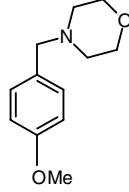
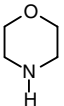
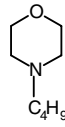
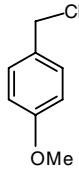
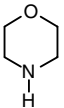
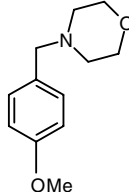
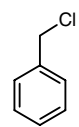
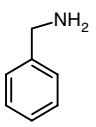
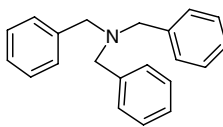
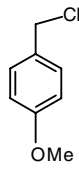
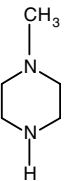
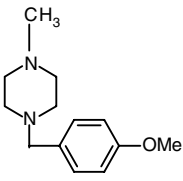
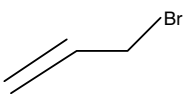
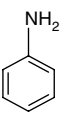
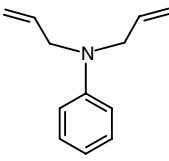
Entry	Halide	Amine	Product amine	Time (h)	Isolated yield (%)
1				5	70
2				4	85
3				7	65
4				2	85
5	$n\text{-C}_6\text{H}_{13}\text{Br}$			3	80
6				7	72
7	$n\text{-C}_6\text{H}_{13}\text{Br}$			4	90
8				1	75
9				4	80
10	$\text{C}_2\text{H}_5\text{Br}$			2	95

Table 4 (continued)

Entry	Halide	Amine	Product amine	Time (h)	Isolated yield (%)
11	C <sub>4</sub> H <sub>9</sub> Br			4	65
12	C <sub>4</sub> H <sub>9</sub> Br			2	85
13				1	74
14	C <sub>4</sub> H <sub>9</sub> I			3	90
15				1	68
16				2	75
17				1	90
18				1	85

Reaction conditions; amines (10 mmol), halides (10 mmol), catalyst 20 wt% of amines in acetonitrile (10 mL) at room temperature (30 °C) (for entries 4, 6 and 16, a halide: amine ratio 2:1 has been used).

All products were characterized spectroscopically (IR, <sup>1</sup>H NMR and MS) and showed physical and spectral data in accordance with their expected structure and by comparison with authentic samples.

All compounds are reported [18,29,30].

As shown by the data reported in Table 4, the product yields and the selectivity depends both on the nature of the substrate and on the type of leaving group. Activated

halides (allyl bromide and *p*-methoxy benzyl chloride) with *N*-methyl piperazine and *p*-methoxy benzyl iodide with morpholine reacts in relatively short times.



Table 5  
Recyclability of Al<sub>2</sub>O<sub>3</sub>–OK in the *N*-alkylation of piperidine with benzyl bromide

Sr. no.	Cycle	Yield (%)
1	0	85
2	1	83
3	2	84
4	3	82
5	4	81
6	5	82

Reaction conditions: piperidine (10 mmol), benzyl bromide (10 mmol), catalyst 20 wt% of amines in acetonitrile (10 mL) at room temperature (30 °C), time = 4 h.

#### 4. Recycling studies

Reusability of the catalyst was tested by carrying out repeated runs of the reaction on the same batch of the catalyst system. After each cycle the catalyst was filtered off, washed with acetone, and activated for 120 °C then used for successive cycles. It was observed that the activity of Al<sub>2</sub>O<sub>3</sub>–OK did not decrease considerably even after five cycles (Table 5). Thus, the catalyst Al<sub>2</sub>O<sub>3</sub>–OK found to be recyclable.

#### 5. Leaching experiment of Al<sub>2</sub>O<sub>3</sub>–OK

The percentage of Al and K was analysed by ICP analysis and found to be (Al = 27.00%; K = 39.12%). Leaching experiment of the metal ion and a possible contribution by the resulting homogeneous catalysis was ruled out by the following experiment. The catalyst was filtered at early stage of the reaction (Table 4, entry 2, *t* = 1 h, 30% yield of the *N*-alkylated product) and the reaction was allowed to proceed in the filtrate. We observed that the reaction did not proceed further in the solution and the yield of *N*-alkylated product remained 30%. This proved that there was no significant leaching of the Al and K ions to make the reaction homogeneous. Therefore, we concluded that the reaction was truly heterogeneous in nature.

#### 6. Conclusion

In conclusion, a direct *tert*-amine forming protocol has many obvious advantages, compared to those reported in literature. These include high selectivity, room temperature, higher yields, being environmentally more benign and the potential for recycling of the catalyst.

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