

SHORT COMMUNICATION

A novel method for *N*-alkylation of aliphatic amines with ethers
over γ - Al_2O_3 ^{a,b}Hangeng Chen, ^aTao Zhang, ^aChao Qian*, ^aXinzhi Chen^aDepartment of Chemical and Biochemical Engineering, Zhejiang University, Hangzhou 310027, China^bSINOPEC Jinling Company, Nanjing, 210033, China

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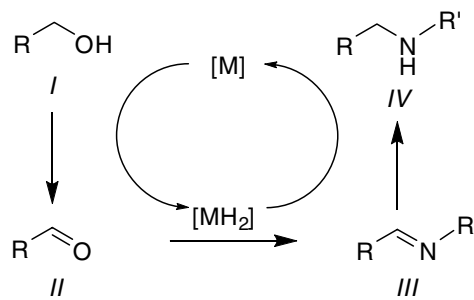
A novel and simple method for the *N*-alkylation of amines with different ethers as alkylating reagents has been developed, using cheap γ - Al_2O_3 as the catalyst at atmospheric pressure in the temperature range of 260–320 °C. For example, the reaction of equimolar amounts of morpholine and diethyl ether gave *N*-ethylmorpholine quantitatively. The present catalytic system is applicable to the *N*-alkylation of both primary and secondary amines. Since only water is generated as byproduct, the protocol proved to be eco-friendly and atom-economic.

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The development of versatile and efficient methods for the synthesis of amines is now an active area of research (Chiappe & Pieraccini, 2003) as a variety of amines are widely used as chemical intermediates to prepare solvents, fine chemicals, agrochemicals, pharmaceuticals, and catalysts for polymerization. The reactions of amines have been a topic of immense research interest due to the synthetic utility and biological activity of their products (Gawande et al., 2007). Among these, *N*-alkylation of amines is recognized as a very important reaction in organic synthesis.

Alkylation with alkyl halides or their equivalents (e.g. dialkyl sulfates or dialkyl sulfonates) is the most conventional method (Romera et al., 2004). A review on the methods available for the preparation of different secondary amines has been published (Salvatore et al., 2001). Although the conversion appears simple, the synthetic method is limited due to selectivity problems such as the generation of multialkylated amines as the reaction of a primary amine with an alkyl halide occurs when control multiple alkylation becomes difficult and it is always undesirable from an environmental point of view as equimolar amounts of waste salts are generated.

**Fig. 1.** Borrowing hydrogen process.

Alkylation of amines can also be accomplished by a primary or a secondary amine with an alcohol as the reagent in the presence of a hydrogenation/dehydrogenation catalyst (Baiker & Kijenski, 1985; Hargis, 1990). The process can be defined as “hydrogen autotransfer” or “borrowing hydrogen process” (Fig. 1) (Guillena et al., 2007; Hamid et al., 2007; Nixon et al., 2009).

This process involves three well-known reactions. Firstly, alcohol *I* is oxidized into a carbonyl compound, *II*, with a metal catalyst [M]; in the next step, carbonyl

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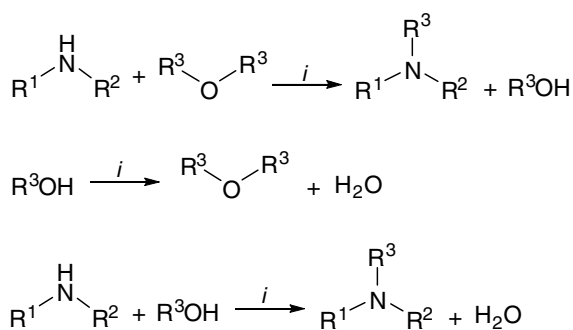


Fig. 2. Possible reactions during the *N*-alkylation process. Reaction conditions: *i*) $\gamma\text{-Al}_2\text{O}_3$, $T = 260\text{--}320^\circ\text{C}$, gas-phase. $\text{R}^1 = \text{alkyl}$, $\text{R}^2 = \text{alkyl or H}$, $\text{R}^3 = \text{alkyl}$.

intermediate *II* is attacked by an amine nucleophile to yield an imine, *III*, which is finally hydrogenated generating thus amine *IV* (Dobereiner & Crabtree, 2010). Water is the only waste generated. Moreover, low molecular mass of the waste makes this synthetic strategy unbeatable as far as the atom efficiency numbers are concerned (Guillena et al., 2010). Several reviews cover the use of the hydrogen autotransfer process for the preparation of amines (Guillena et al., 2010; Nixon et al., 2009). Different transition metals have been proposed as catalysts for this process, including those derived from nickel (Winans & Adkins, 1932), copper (Baiker & Richarz, 1977), rhodium (Watanabe et al., 1981), ruthenium (Marsella, 1987). The major drawback of this methodology is that they always proceed in a homogeneous phase, where complex separation processes removing and recycling the expensive transition catalyst take place (Salvatore et al., 2001). Furthermore, processes for the preparation of catalysts are always tedious (Narayanan & Deshpande, 2000; Hamid & Williams, 2007). Compared with the homogeneously catalyzed reaction, the alkylation of amines with alcohols in gas or liquid–solid heterogeneous phases using metal or metal oxide catalysts such as silica gel (Brown & Reid, 1924), $\gamma\text{-Al}_2\text{O}_3$ (Valot et al., 1999; Li & Peng, 1994; Ko et al., 1996), or unmodified magnetite (Martínez et al., 2009) allows easier separation of catalysts and products. These procedures are applicable for a large number of alcohols and amines. As additional benefits, the reaction conditions are always solvent-free and cheap silica gel or $\gamma\text{-Al}_2\text{O}_3$ offer a suitable replacement for costly transition metal catalyst.

Since there are only a few examples describing the alkylation of aliphatic amines in the literature (Salvatore et al., 2001), the aim was to present herein a novel and simple method for the *N*-alkylation (mono- and dialkylation) of amines (both aliphatic and heterocyclic) with different kinds of ethers as alkylating agents and using cheap $\gamma\text{-Al}_2\text{O}_3$ as the catalyst at atmospheric pressure in the temperature range of 260–320 °C (Fig. 2).

$\gamma\text{-Al}_2\text{O}_3$ ($S_{\text{BET}} = 220\text{--}250 \text{ m}^2 \text{ g}^{-1}$, $\Phi = 1\text{--}2 \text{ mm}$; metallic impurities: Na, Si, Ca, Fe < 4 mg kg⁻¹) was supplied by Wenzhou Jingjing Aluminum Co., Ltd., China. Amines and other standard samples were all purchased from Hangzhou Huadong Medicine Co., Ltd., China. Reagents were dried over 4 Å molecular sieves and purified by distillation when necessary. The products were analyzed by an Agilent 1790F gas chromatograph (GC) with a hydrogen flame ionization detector and a glass column (45 m × 0.53 mm).

A pilot plant for the alkylation of amines, which could be heated by the jacket filled with salt bath, consisted of a fix-bed with liquid, gas inlets on the top and products outlet at the bottom. The catalyst was fixed in the middle of the bed, quartz was used as a sizing agent. Total height of the reactor, H_T , was 60 cm and the diameter of the effective column, D_c , was 30 mm. Effective reacting length and volume, L_T , V_T , were 40 cm and 0.2–0.25 m³, respectively. The catalyst bed worked steadily in a wide range of process conditions.

General procedure for the *N*-alkylation of amines: amine/ether mixture is introduced via the liquid feeders on the top of the vertical reactor at the flow rate of 0.8 mL min⁻¹, with nitrogen as the carrier gas (60 L h⁻¹); the reactor is heated to the desired temperature and then maintained by the jacket filled with salt bath; reagents are allowed to pass through the catalyst bed and the products are condensed in 1–2 h in an ice bath at the bottom of the reactor. Concentration of the products was detected by GC compared with a standard sample. The alkylated product was confirmed by comparison with the standard sample using GC or literature data of ¹H or ¹³C NMR (Heydari et al., 2007; Nacario et al., 2005; Ouk et al., 2005; Kawaguchi et al., 1985; Adima et al., 2004; Takasaki et al., 2007; Lai, 1980; Suzuki et al., 1983).

Alkylation of several primary or secondary aliphatic and heterocyclic amines was tested using diethyl ether as the alkylating reagent (Table 1). The results indicated that the conversion of amines, independent of the amine itself, increased with higher temperature and mole ratio (ether/amine). When conversions were relatively low, the reactions were highly directed towards the monoethylated products whereas the diethylated ones were formed preferentially at higher conversions. Diisopropylamine gave poor conversion and did not react with the increasing temperature, probably due to the steric effects. On the contrary, cyclohexylamine and morpholine lead to good selectivities in monoalkylated products even at high conversions and temperatures. With respect to cyclohexylamine, at the conversion of 97 %, monoalkylated amine was formed preferentially, which changed little with temperature.

Other ethers with different amines were tested in the same reaction (Table 2). Owing to the steric effects, diisopropyl ether gave a conversion as low as

Table 1. *N*-Alkylation of different amines with diethyl ether

Amine	<i>T</i> /°C	Conversion/%	Selectivity/%	
			R ¹ NHEt	R ¹ NEt ₂
Butylamine	260 ^a	78	84	16
	300 ^a	90	69	31
	320 ^b	99	21	79
Diisopropylamine	280 ^a	5	100	–
	320 ^a	8	100	–
	360 ^b	9	100	–
Morpholine	270	100	100	–
Cyclohexylamine	260 ^a	89	87	13
	300 ^b	97	85	15

a) Diethyl ether to amine mole ratio = 1.05 : 1; b) diethyl ether to amine mole ratio = 2 : 1.

Table 2. *N*-Alkylation of different amines with different ethers

<i>T</i> /°C	Ether	Amine	Conversion/%	Selectivity/%	
				Monoalkylation	Dialkylation
280	Diisopropyl ether	Butylamine	39	93	2
		Morpholine	48	100	–
320	Methyl <i>tert</i> -butyl ether	Morpholine	79	78 ^a , 12 ^b	–
		Cyclohexylamine	47 ^b	55 ^a , 10 ^b	25 ^c
300	Dipropyl ether	Diisopropylamine	14	96	–
		Morpholine	97	100	–

a) Product of *N*-methylation; b) product of *N-tert*-butylation; c) dimethylated product; ether to amine mole ratio = 1 : 1.

diisopropylamine. Many *N-tert*-butylamines are not easily prepared by *N*-alkylation of amines with *tert*-butyl alcohol. However, in this paper, the formation of *N-tert*-butylamines is considered in regard of some amines difficult to be prepared by conventional methods, such as *N-tert*-butylmorpholine and *N-tert*-butylcyclohexylamine.

One of the advantages of vapor phase catalysis is the solvent-free conditions. In our case, one of the reaction components can serve as both diluent and reagent. Ether was both solvent and reagent in this paper, and the ratio of ethers and amines could even be decreased to stoichiometric maintaining the same selectivities at the same conversion. It can be explained by the change of the alcohol produced in the *N*-alkylation process to the corresponding ether by dehydration and its reuse in further alkylation reactions, except some tertiary alcohols (Fig. 2), or its use directly as the *N*-alkylating reagent. Since ethers and alcohols can be both detected by GC, it was still unclear which of them was the real alkylating agent. The only byproduct was water. Otherwise, in all cases, GC analysis clearly showed that no disproportionation of

straight-chain aliphatic amines occurred during the reaction, even at the maximum temperature of 320 °C.

Our method appears all the more attractive as some *N*-alkylated amines cannot be prepared by dehydration of alcohols with amines, e.g. *N-tert*-butylamines, without any side reactions. From an industrial point of view, pure amines could be obtained from the products by distillation. Since the alcohol can be recycled, the whole process complies with the green-chemical concept.

In conclusion, a new catalytic method suitable for mono- or dialkylation of amines with ethers without any other side reactions, e.g. disproportionation of straight-chain aliphatic amines, is presented. Some amines difficult to be prepared by the general method can also be obtained. The conditions of gas-phase catalysis can be successfully applied to fine chemistry.

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