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Gas-phase selective N-alkylation of amines with alcohols over γ-alumina

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Abstract

Gas-phase conditions were successfully used for fine chemistry, in the N-alkylation of amines with alcohols as alkylating agents and γ-alumina as a catalyst. The method is also suitable for chiral compounds.

Keywords : gas-phase synthesis; N-alkylation of amines; alcohols; chirality.

Since the beginning of the 90's with the seminal articles of Trost [1,2] and Sheldon [3], the attention of the organic chemists was drawn to the necessity to develop methods in agreement with the atom economy concept to fit with increasing environmental awareness. It is thus necessary to minimize or, if possible, to eliminate the waste production. A complete rethinking of the strategy in organic synthesis should be undertaken. To solve this waste problem, one should, notably, use more catalysis in organic synthesis, limit the utilization of hazardous and/or toxic chemicals and reexamine the question of solvent (nature and necessity). In this article we want to show that gas-phase catalysis fits with most of these criteria and could be applied successfully to classical organic reactions. As an example, we examine the possibility to perform selective N-alkylation of amines by this method.

The N-alkylation of amines is an important reaction in organic synthesis. Alkylation with alkyl halides is the most conventional method [4] but it generates salts as by-products and exhibits often low chemical selectivity. Other reagents such as diazomethane [5] dialkylcopperlithium [6] or dialkylphosphites [7] were also used for the same purpose but they are dangerous to handle or lead to purification problems. The reductive amination procedure [8] is also a suitable method to perform N-alkylation with carbonyl compounds. Several reductors have been used among which hydrogen [9] and sodium borohydride with titanium isopropoxide [10]. Nevertheless, these conditions are not always selective for mono N-alkylation of primary amines. Alcohols have also been used as alkylating agents with Ni [11] Rh or Ru catalysts [12-14]. All these methods eventhough selective proceed in homogeneous phase and tedious separation procedures are necessary to remove and recycle the catalyst.

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The principle of direct alkylation of amines with alcohols is known since the beginning of the century. Thus, in 1909, Sabatier [15] reported the first N-alkylation of amines with alcohols over ThO_2 catalyst. Nevertheless, the reaction conditions were difficult to apply to fine chemistry. Indeed, the reaction took place in a sealed tube placed in a Bunzen flame. More recently, several articles and patents have appeared on the subject in the litterature but generally only aniline derivatives were extensively studied using zeolites [16], silica supported vanadia catalysts [17] or γ-alumina [18-20] in a fixed-bed integral-flow reactor at atmospheric pressure. There are only few examples describing the alkylation of aliphatic amines with alcohols [21] : to our knowledge, only one example is described (methylation of butylamine with methanol) and the selectivity is directed only towards the dimethylated product.

Unlike what is described in the litterature, we want here to report an easy and selective method for the N-alkylation of amines (aromatic or aliphatic, mono- or di-alkylation) with a large scope of alcohols and amines, using the cheap γ-alumina as a catalyst at atmospheric pressure in a temperature range of 200-300°C (equation 1). We also want to show that chiral amines are not modified after reaction by this method.

$$R\text{-}NH_2 + R'OH \xrightarrow[\text{gas-phase}\\ 200\text{-}300^{\circ}C]{\gamma\text{-}Al_2O_3} RNH\text{-}R' + RNR'_2 + H_2O \qquad (1)$$

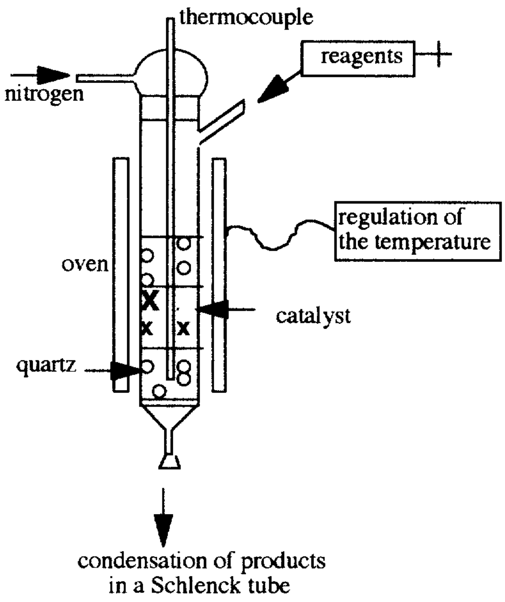
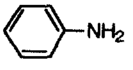
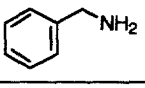
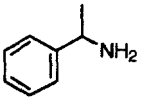


Figure 1 : continuous-flow reactor.

Several primary amines have been tested with methanol as alkylating agent (Table 1). Whatever the amine, conversion logically increases with temperature. At low conversions, the selectivities are high in monomethylated products whereas dimethylated ones are preferentially formed at higher conversions. Nevertheless, with aniline a selectivity of 90% in N-methylaniline is obtained at 45% conversion.

One of the advantages of vapor phase catalysis is the possibility to work without solvent. In our case, the alcohol is both diluent and reagent. We can decrease the alcohol/amine ratio : the selectivities remain unchanged at equal conversion. It is nevertheless necessary to increase the temperature of 25°C, when the ratio is reduced from 300 to 20, to have the same amine conversion. Other alcohols were tested in the same reaction (Table 2).

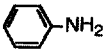
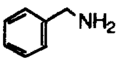
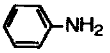
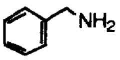
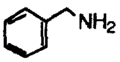
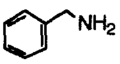
Table 1
Different amines N-alkylated by methanol.

Entry	Amine	T (°C)	Conversion (%)	Selectivity R-NHMe (%)	Selectivity $R\text{-}NMe_2$ (%)
1	$C_8H_{17}NH_2$	280	94	10	90
		290[a]	91	8	92
2		200	45	90	10
		320	99.5	5	85[b]
3		220	48	52	48
		270	95	28	60
4		250	37	79	13[c]

Conditions : methanol/amine = 300.
a : methanol/octylamine = 100.
b : 10% of dimethylaniline methylated at an undefined position on the aromatic ring are detected.
c : 8% of styrene are formed.

Whatever the amine, isopropyl alcohol gives rise to poor conversion, probably due to steric effects. Nevertheless, as the separations of the N-isopropyl aniline or benzylamine from the reaction mixture are easy, these results could be interesting in regards of the high selectivities. On the contrary, 1-propanol and 1-hexanol lead to good selectivities in monoalkylated product even at high conversion. With benzylic alcohol, at 100% conversion, the tertiary amine is preferentially formed. This could be due to the easier formation of the supposed benzylic cation intermediate.

Table 2
Different alcohols as N-alkylating agents of amines.

Entry	T (°C)	Alcohol	Amine	Conversion (%)	Selectivity (%) monoalkylation	Selectivity (%) dialkylation
1	300	1-propanol		80	90	9
					77[a]	5
2	230	2-propanol		8	96	1
					80	20
3	290	1-hexanol		92	72	14
4	290	benzylic alcohol		100	19	78

Conditions : alcohol/amine = 20.
a : 18% of N-propylbenzylamine with a propyl group on the aromatic ring are formed.

During the reaction, dialkylether is also formed. Experiments performed without alcohol but with dialkylether as reagent and diluent, lead to similar N-alkylation reactions. Thus, although it is still unclear what is the real alkylating agent, this ether formation is not a problem as the mixture ether-alcohol can be recycled and used in further alkylation reactions.

Experiments were also performed on enantiomerically pure α-methylbenzylamine. GC analysis (on a CYDEX-B capillary gas chromatography column) clearly showed that no racemization occured during the reaction, even at temperatures like 300°C, which has, as far as we know, never been reported before. Obtention of chiral secondary amines with high optical purity is most of the time laborious [22]. Our method appears all the more competitive since monomethylation can not be obtained by using reductive alkylation.

In a typical procedure, the amine/alcohol mixture is introduced *via* a syringe on top of a vertical continuous-flow reactor (2 ml/h) using nitrogen as a carrier gas (20 ml/min). The reagents are allowed to pass through the catalyst (2 g γ-Al_2O_3 [23]). The reactor is put into an oven where temperature is regulated. The reaction products are condensed during 1 h in an ice bath at the bottom of the reactor (Figure 1). N-propylaniline (entry 1 Table 2) was isolated by removal of the alcohol under reduced pressure with 50% yield (theoretical 62%, 91% pure). N,N-dimethyloctylamine (entry 1, Table 1) was firstly treated with HCl and then isolated identically. The corresponding ammonium salt was obtained 90% pure from NMR (350 mg) with 76% yield (theoretical 89%). In both cases, ^1H and ^{13}C NMR spectra were found consistent with literature data. From an industrial point of view with larger quantities of products, the isolation would be obtained by vacuum distillation.

In conclusion we have described here a new catalytic method suitable for the mono- or di-alkylation of amines with cheap reagents (alcohols), producing only water as by-product and compatible with chirality. High temperature gas-phase catalysis can be applied successfully to fine chemistry and studies are in progress to enlarge the scope of reactions in such conditions.

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