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Short Communication

Solid base catalyzed highly efficient *N*-alkylation of amines with alcohols in a solvent-free system

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ABSTRACT

Different from any other catalytic systems containing transition metals and additives, sodium hydroxide itself was found to be a unique and effective catalyst for the solvent-free synthesis of the secondary amines *via* the *N*-alkylation of amines with alcohols. For the reaction of aniline with benzyl alcohol, 99.6 mol% conversion of aniline and 99.5% selectivity of the product were achieved under optimal conditions. Also, high conversion and selectivity could be acquired for the *N*-alkylations of various amines with alcohols, implying the universality of this methodology. Mechanistic studies revealed that this novel reaction most possibly proceeds with a base-catalyzed mechanism.

1. Introduction

Amines and their derivatives are prevalent functionalities in various natural products and unnatural synthetic targets [1–3]. Many different ways to alkylated amines have been developed, including reductive methods for imines [4], amides [5], and direct alkylation by halide [6], sulfonate [7] or hydrogenating amination of alkynes or alkenes with primary or secondary amines [8]. In these methods, the most classical one used for the alkylation of amines is the reaction with alkyl halides or related alkylating agent in the presence of a stoichiometric amount of base. However, this approach suffers from drawbacks such as low atom efficiency, low selectivity, producing over-alkylated *di* and quaternary amines as wastes [9]. Thus, more and more chemical researchers start to use alcohols as intoxic, inexpensive and readily available alkylation reagents.

Initially, the *N*-alkylation of amines with alcohols was carried out in the presence of homogeneous catalysts, such as ruthenium- [10], iridium- [11], palladium- [12], aurum- [13], or platinum-based complexes [14], with which excellent results were obtained. Since 2009, ruthenium-, palladium-, platinum-, gold-, silver-, nickel-, manganese-, and iron-based heterogeneous catalysts have been studied [15]. Recently, heterogeneous non-noble metal catalysts have been reported, inclusive of the supported copper catalysts, Ni-Cu/Al_2O_3 catalyst and NiCuFeOx catalyst [16–19], which, however, require solvent, basic promoter, long reaction time, or high pressure equipment.

In our previous work [20], the basic promoter played a key role in activating the synthesis of imines from amines and alcohols over Co-13X. However, the present work shows that only simple solid base could effectively catalyze the *N*-alkylations of amines and alcohols to produce the secondary amines, which may demonstrate the base-catalyzed nature of this kind of *N*-alkylations of amines with alcohols.

2. Experimental

2.1. Materials

All organic reagents inclusive of aromatic alcohols, aliphatic alcohols, aromatic amines, and cyclohexylamine were directly used without further purification, but aniline underwent re-distillation under reduced pressure to obtain a purity of 99.9%.

2.2. Structural characterization of products

Melting points were determined by a Shimadzu DSC-60 differential scanning calorimeter in the range of room temperature-673 K. Mass spectra were recorded on an Agilent 1260-6224 LC-MS TOF. Elemental analyses (C, H, N) were conducted on an Elementar VarioEl-III instrument. NMR spectra were measured using a Bruker WIPM 400 or INOVA 600 spectrometer at 600 MHz (^{1}H) and 150 MHz (^{13}C). All NMR spectra were recorded at room temperature in $CDCl_3$ unless otherwise noted and chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS).

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2.3. General procedure

All the reactions were carried out in a glass flask heated with a temperature-programmed furnace. Typically, 4.0 mmol of amine, 40.0 mmol of alcohol, and 40 mg of solid base were sequentially added to a glass flask (25 ml). Then, the reaction mixture was vigorously stirred under air atmosphere by a magnetic stirrer and heated to desired temperatures, which were then kept for 6 h. After the completion of reactions, the reaction mixture was cooled down to room temperature and dissolved with 10 ml of dichloromethane. The solid catalyst was filtered off by centrifuge from the liquid phase. The liquid mixture was analyzed by gas chromatograph (Shimadzu GC-2010) with a DB-1 column (30 m × 0.25 mm × 0.25 μm) and an FID detector. In order to obtain the corresponding *N*-substituted amines from the reaction mixture, the crude reaction mixture was concentrated in vacuo and purified by column chromatography. In the latter case, the flowing phase was consisted of petroleum ether (b.p. 60–90 °C)/ethyl acetate/triethylamine.

3. Results and discussion

3.1. N-alkylation of aniline with benzyl alcohol over solid base

In order to optimize the reaction conditions, we chose the N-alkylation of aniline with benzyl alcohol as a model reaction (Scheme 1).

When different bases were used in the reaction of Scheme 1, the selectivity of imine 3 displayed a significant variation. Especially, when solid sodium hydroxide was added, the selectivity of imine 3 dropped abruptly to 30.3%, while the selectivity of amine 4 rose to 69.7%, which caught our attention.

We discovered that only solid sodium hydroxide could catalyze the conversion of 99.6 mol% aniline ($PhNH_2$) to achieve 99.5% selectivity of amine 4 at 493 K in the case of excess benzyl alcohol ($PhCH_2OH$). Note that no any transition metal or additive was used, notably different from the cases in the literature [10–19]. When no base was added, only 31.7 mol% of aniline was converted with 94.3% selectivity of imine 3. Of various bases tested in Table 1, solid NaOH was the most active, offering 99.6 mol% conversion of aniline with 99.5% selectivity of amine 4. Other bases such as sodium carbonate, sodium bicarbonate, sodium acetate, potassium carbonate, and cesium carbonate afforded very poor selectivities to the secondary amine 4, presumably due to weak basicity. Sodium amide, sodium methylate, and potassium *tert*-butoxide merely offered 65.1–85.6% selectivity of amine 4. Although 97.2 mol% conversion of aniline was obtained over KOH, the selectivity of the secondary amine 4 was 84.4%, ascribable to its strong basicity unfavoring the formation of amine 4.

Along with increasing the base amount from 0 to 1.0 mmol, the conversion of aniline and the selectivity of amine 4 were gradually increased to 99.6 mol% and 99.5%, respectively (Fig. S1). The excess base would no longer make a further contribution. The optimal molar ratio of aniline to benzyl alcohol was about 1: 10 (Fig. S2), favorable for high conversion and selectivity. As seen from Fig. 1A, the aniline conversion was increased from 65.5 to 99.6 mol% with increasing the reaction temperature from 443 to 493 K. The selectivity to amine 4 was drastically increased from 38.2% at 443 K to 99.5% at 493 K. Too high temperature would enhance side reactions, while too low temperature was unfavorable to the formation of amine 4. The conversion of 17.9 mol% and the selectivity of 40.4% were achieved in 15 min (Fig. 1B); those were linearly increased to 38.8–69.1 mol% and 49.5–82.7% within 4 h. When the reaction time was prolonged to 6 h, both values could reach 99.6 mol% and 99.5%, respectively. With increasing the reaction time to 10 h further, the conversion of aniline was kept in the level of 99.0–99.2 mol%, but the selectivity of the secondary amine 4 was reduced to 96.4–93.9%.

Table 1
Influence of different alkalis.

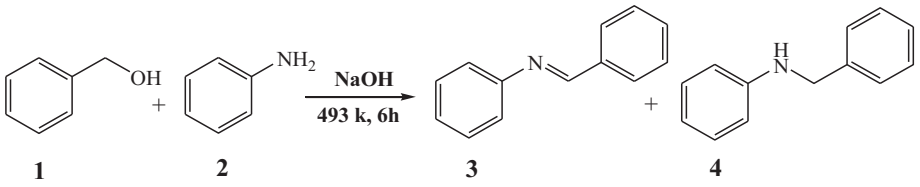
Entry	Base	Conversion[a] (mol%)	Selectivity (%)	
			3	4
1	No	31.7	94.3	5.7
2	NaOH	99.6	0.5	99.5
3	$NaNH_2$	90.2	7.0	85.6
4	CH_3ONa	84.0	35.5	64.5
5	Na_2CO_3	41.6	86.0	12.2
6	$NaHCO_3$	39.0	91.8	8.2
7	NaAc	36.7	86.8	13.2
8	KOH	97.2	15.1	84.4
9	Bu^tOK	78.2	34.5	65.1
10	K_2CO_3	69.7	66.7	33.3
11	Cs_2CO_3	74.5	69.8	30.2

Reaction conditions: amine (4 mmol), alcohol (40 mmol), NaOH (1 mmol), temperature 493 K, time 6 h.
[a] Values are conversion with respect to aniline.

3.2. N-alkylation of various amines with alcohols over solid NaOH under optimal conditions

Under optimal conditions, *N*-alkylations of a number of structurally diverse amines and alcohols over solid NaOH were tested (Table 2). Aromatic amines containing electron-donating and electron-withdrawing groups in entries 1–5 could readily react with benzyl alcohol to give mono-*N*-alkylated amine products in very good yields. Also, 2-aminopyridine and cyclohexyl amine as substrates could selectively yield the targeted amines. In these reactions, the selectivity of byproduct imines was obviously reduced. As attached in the supporting information, five secondary amine products in Table 2 have well been separated and purified by traditional column chromatography, and structurally characterized by melting points, ^1H and ^{13}C NMR spectra, elemental content analysis, and mass spectroscopy. These characterizations further confirmed the effectiveness of our present system on the formation of *N*-alkylated secondary amines from amines and alcohols over solid base.

However, the reactions between other amines and alcohols achieved low conversions, or low selectivities, or low conversions and selectivities even under the optimal reaction temperatures (in Table 2). These experimental observations propose that the actual occurrence of reactions may be affected by various factors, inclusive of the electron effects of the substituting groups attached to rings, spatial hindrance in transition states, and boiling points of substrates.



Scheme 1. N-alkylation of aniline with benzyl alcohol as a model reaction.