## Colloid and Nanodimensional Catalysts in Organic Synthesis: III.<sup>1</sup> Alkylation of Amines with Primary Alcohols Catalyzed by Colloidal Nickel and Cobalt

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**Abstract**—Alkylation of primary amines with primary alcohols has been performed under catalysis by colloidal nickel and cobalt particles. The synthesis of the catalyst and alkylation of amines have been carried out in a one-pot mode. The alkylation at 160–180°C in 6–12 h yields 55–90% of secondary amines.

**Keywords:** alkylation, catalyst, nanoparticles, amines, alcohols

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Amines are generally alkylated with alkyl halides at elevated temperature [2]. However, this method is not free from some disadvantages related to low accessibility and toxicity of many alkyl halides and the necessity of utilizing hydrogen halides formed during the process. Alkylation of amines with alcohols in the presence of conventional catalysts, such as aluminum oxide or mixed metal oxides, requires fairly harsh conditions, including the use of gaseous hydrogen under high pressure and elevated temperature (as a rule, not lower than 200°C) [3, 4]. Moreover, this reaction leads to the formation of mixtures of secondary and tertiary amines at different ratios. Alkylation of amines with alcohols under catalysis by ruthenium [5, 6] and iridium complexes [7, 8] has been reported. However, the use of these procedures is limited due to complexity of preparation of the catalysts and their high cost. Alkylation of amines in the presence of accessible nickel powder or Raney nickel requires considerable amounts of the catalyst [9].

Kwon et al. [10] described alkylation of amines over palladium nanoparticles under mild conditions, which afforded 75–90% of secondary amines. Kegnaes et al. [11] reported on the synthesis of imines by oxidative cross-coupling of amines with alcohols catalyzed by titanium dioxide-supported gold nanoThe available published data suggest importance of studies directed toward search for accessible catalytic systems that could ensure synthesis of secondary amines via alkylation of primary amines with alcohols under as mild conditions as possible.

As catalysts we tried ultrafine cobalt and nickel particles. Colloidal solutions of these metals were prepared according to known procedures. Nickel nanoparticles capable of forming a homogeneous colloidal solution were obtained by reduction of nickel salts with hydrazine hydrate in aqueous–alcoholic medium [15, 16]; the size of the metal particles was less than 20 nm. We were the first to accomplish direct alkylation of amines **Ia–Ie** with alcohols **IIa–IIc** in the presence of colloidal cobalt or nickel particles without their stabilization in the reaction mixture. We thus obtained the corresponding secondary amines in 55–87% yield (see Scheme 1).

particles [11]. Among more accessible and less expensive catalysts, copper–nickel particles stabilized by barium stearate were used to catalyze amine alkylation at temperatures exceeding 210°C [12]. Supported iron nanoparticles showed high efficiency in the alkylation of amines with alcohols under microwave irradiation [13]. Alonso et al. [14] reported on the alkylation of aniline derivative with various alcohols in the presence of nickel nanoparticles to obtain secondary amines.

<sup>&</sup>lt;sup>1</sup> For communication II, see [1].

$$\begin{array}{rcl} & \text{Scheme 1.} \\ \text{RNH}_2 &+ & \text{R}^1\text{OH} & \xrightarrow{\text{Ni}^0(\text{Co}^0)} & \text{RNHR'} &+ & \text{H}_2\text{O} \\ \hline & \text{Ia-Ie} & \text{IIa-IIc} & \xrightarrow{\text{II60-180}^\circ\text{C}} & \text{IIIa-IIIg} \end{array}$$

 $R = Ph, R' = PhCH_2$  (Ia, IIa, IIIa),  $C_6H_{13}$  (IIb, IIIb),  $C_8H_{17}$  (IIc, IIIc);  $R = PhCH_2, R' = PhCH_2$  (Ib, IIId);

$$\mathbf{R} = \begin{bmatrix} \mathbf{N} \\ \mathbf{R} \end{bmatrix}, \ \mathbf{R}' = \mathbf{C}_{6}\mathbf{H}_{13} \ (\mathbf{Ic, IIIe}); \ \mathbf{R} = \begin{bmatrix} \mathbf{N} \\ \mathbf{R} \end{bmatrix}, \ \mathbf{R}' = \mathbf{C}_{6}\mathbf{H}_{13} \ (\mathbf{Id, IIIf}), \ \mathbf{R} = \begin{bmatrix} \mathbf{C}_{13} \\ \mathbf{C}\mathbf{H}_{2} \end{bmatrix}, \ \mathbf{R}' = \mathbf{PhCH}_{2} \ (\mathbf{Ie, IIIg}).$$

Scheme 2.



Our experiments showed that the reaction requires heating to 160°C and above; therefore, the developed liquid-phase procedure is applicable to high-boiling alcohols and amines.

Nickel nanoparticles showed a higher catalytic activity than cobalt nanoparticles in the alkylation of amines with primary alcohols. In order to increase the selectivity and the yield of secondary amines it was necessary to use 1.5–2 equiv of alcohol with respect to the amine; the reactions with equimolar amounts of the reactants were characterized by incomplete conversion, and by-products (including imines) were formed. In the presence of a large excess of alkali the yields of tertiary amines were insignificant.

The yields of secondary amines **IIIa–IIIg** depended on the amount of the catalyst. It was necessary to use at least 10 wt % of the catalyst to ensure efficient alkylation, and the best yields of secondary amines in the shortest time were obtained when the amount of the catalyst was 25–30 wt % with respect to primary amine. The process is accompanied by agglomeration of the catalyst particles, which leads to reduction of their specific surface area and hence catalytic activity, so that considerable amounts of the catalyst are required.

The structure of secondary amines **IIIa–IIIg** was confirmed by <sup>1</sup>H NMR and GC/MS data. Their <sup>1</sup>H NMR spectra contained signals from protons in the benzene ring and alkyl group, and protons in the

methylene group attached to nitrogen resonated at  $\delta$  2.8–3.0 ppm. The properties of previously described compounds were consistent with published data.

In keeping with published data [17, 18], a probable reaction mechanism may be illustrated by the Scheme 2.

Alcohol is oxidized to the corresponding aldehyde on the catalyst surface, and the aldehyde reacts with amine to give Schiff base which is reduced to secondary amine with adsorbed hydrogen. Analogous mechanism for the catalysis by metal complexes is referred to as "borrowing hydrogen methodology" or "hydrogen autotransfer" [17, 18]. The proposed mechanism is confirmed by the <sup>1</sup>H NMR spectra of the reaction mixture obtained with a small excess of alcohol, which contained a signal at  $\delta \sim 6.0$  ppm due to the CH=N proton in intermediate imine.

According to the GC/MS data, the alkylation catalyzed by colloidal cobalt particles was accompanied by disproportionation of amines. With a view to verify this reaction path, we successfully accomplished disproportionation of benzylamine in the absence of alcohol (Scheme 3). The reaction was carried out at 130°C and higher temperature (2–4 h), and the yield of dibenzylamine (**IIIg**) was 67%. Likewise, amine **IIIg** was obtained in 78% yield when 18 mol % of nickel nanoparticles was used as catalyst. These data indicate that colloidal nickel particles are more efficient than Raney nickel in disproportionation of amines. Analogous reaction with Raney nickel requires 80–





400 mol % of the catalyst and prolonged (up to 15 h) heating, and the yield of secondary amines amounts to 67-88% [17].

Our results suggest the possibility for crosscoupling of amines catalyzed by metal nanoparticles [18]. The mechanism of this reaction is likely to be similar to the mechanism of amine alkylation with alcohols, i.e., it involves elimination of hydrogen on the metal surface with formation of imine.

We tried to perform cross-disproportionation of primary and secondary amines. Shimizu et al. [19] previously reported on analogous reaction catalyzed by alumina-supported palladium nanoparticles, which ensured a yield of up to 88%. The reactivity of amines is largely determined by their structure and stability of intermediate Schiff bases. The conversion of 1adamantylmethanamine or 2-(1-adamantyl)ethanamine in 6 h at 160°C was insignificant. By GC/MS we detected only  $\sim 2\%$  of the corresponding secondary amines. Cross-coupling of 2-(1-adamantyl)ethanamine with 3 equiv of piperazine was also inefficient. The vield of expected N-[2-(1-adamantyl)ethyl]piperazine was about 1%, and the yield of the primary amine disproportionation product was 2%. Taking into account that the data in [19] were obtained with benzylamine and its derivatives, we can conclude that these amines are considerably more prone to disproportionation than other primary alkylamines.

In summary, we have developed a convenient liquid-phase procedure for the alkylation of primary amines with primary alcohols in the presence of colloidal cobalt and nickel nanoparticles whose considerable specific surface area allows the use of smaller amount of the catalyst. Colloidal metal particles are readily available via reduction of their watersoluble salts, and no stabilization of nanoparticles in the reaction mixture is necessary. Further improvement of the proposed method with a view to increase the yield of secondary amines and reduce the catalyst consumption is challenging.

## EXPERIMENTAL

The <sup>1</sup>H NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz) from solutions in carbon tetrachloride using hexamethyldisiloxane or tetramethylsilane as internal reference. Gas chromato-graphic–mass spectrometric analyses were obtained on a Varian Saturn 2100 T/GC3900 instrument.

Colloidal nickel and cobalt particles were prepared by reduction of nickel(II) and cobalt(II) chlorides or nitrates with hydrazine hydrate in aqueous isopropyl alcohol according to the procedures described in [15, 16]. Insofar as all reactions were carried out at 130– 190°C, the corresponding amine and alcohol were commonly added to a colloidal metal solution, and aqueous isopropyl alcohol was then distilled off.

**N-Benzylaniline (IIIa).** *a*. A mixture of 10.8 g (0.1 mol) of benzyl alcohol, 15 g (0.161 mol) of aniline, and 3 g of colloidal nickel particles was heated for 6 h at 183–184°C. When the reaction was complete, the mixture was filtered from the settled catalyst. The product was isolated by distillation. Yield 7.7 g (0.042 mol, 76.5%), bp 306–307°C; published data [19]: bp 306–307°C. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 3.60 s (1H, NH), 3.86 s (2H, CH<sub>2</sub>), 6.74–7.07 m (10H, C<sub>6</sub>H<sub>5</sub>).

*b*. Likewise, from 6 g (0.055 mol) of benzyl alcohol and 2.8 g (0.03 mol) of aniline using 1.8 g of colloidal cobalt particles (183–184°C, 8 h) we obtained 4 g (0.022 mol, 72%) of compound **IIIa** (isolated by vacuum distillation).

*N*-Hexylaniline (IIIb). A mixture of 30.6 g (0.3 mol) of hexan-1-ol, 14 g (0.15 mol) of aniline, and 4 g of colloidal nickel was heated for 6 h at the boiling point. The product was isolated as described above for IIIa. Yield 23.1 g (0.13 mol, 87%), bp 169–171°C (20 mmHg). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm (*J*, Hz): 0.83 t (3H, CH<sub>3</sub>, *J* = 12.9), 1.20 m (6H, CH<sub>2</sub>), 1.37 q (2H, CH<sub>2</sub>, *J* = 19.5), 2.85 t (2H, CH<sub>2</sub>N, *J* = 14.7), 3.32 s (1H, NH), 6.32–6.99 m (5H, C<sub>6</sub>H<sub>5</sub>). Mass spectrum

(EI, 70 eV), m/z ( $I_{rel}$ , %): 177 (100)  $[M]^+$ , 106  $[M - C_5H_{11}]$  (61). Found, %: C 81.36; H 10.75; N 7.89. C<sub>12</sub>H<sub>19</sub>N. Calculated, %: C 81.30; H 10.80; N 7.90.

**N-Octylaniline (IIIc).** A mixture of 17.2 g (0.132 mol) of octan-1-ol, 7.5 g (0.081 mol) of aniline, and 0.6 g of colloidal nickel particles was heated for 10 h at 185–195°C. When the reaction was complete, the mixture was filtered from the settled catalyst. The product was isolated by vacuum distillation. Yield 11.4 g (0.055 mol, 68.5%), bp 180°C (20 mmHg). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm (*J*, Hz): 0.87 t (3H, CH<sub>3</sub>, *J* 12.4), 1.25 m (10H, CH<sub>2</sub>), 1.51 q (2H, CH<sub>2</sub>, *J* = 18.9), 2.98 t (2H, CH<sub>2</sub>N, *J* = 14.1), 3.39 s (1H, NH), 6.38–7.02 m (5H, C<sub>6</sub>H<sub>5</sub>). Mass spectrum (EI, 70 eV), *m/z* (*I*<sub>rel</sub>, %): 205 (100) [*M*]<sup>+</sup>, 106 [*M* – C<sub>7</sub>H<sub>15</sub>]<sup>+</sup> (34). Found, %: C 81.86; H 11.31; N 6.83. C<sub>14</sub>H<sub>23</sub>N. Calculated, %: C 81.89; H 11.29; N 6.82.

**Dibenzylamine (IIId).** *a*. A mixture of 6 g (0.056 mol) of benzyl alcohol, 4.4 g (0.041 mol) of benzylamine, and 0.8 g of colloidal cobalt particles was heated for 5 h at 185–190°C. When the reaction was complete, the mixture was filtered from the catalyst, and the product was isolated by vacuum distillation. Yield 5.7 g (0.029 mol, 71%), bp 159–162°C (10 mmHg),  $n_D^{20}$  1.5742; published data: bp 160–163°C (10 mmHg) [19],  $n_D^{20} = 1.5745$  [20].

*b*. A mixture of 5 g (0.047 mol) of benzylamine and 0.4 g of colloidal cobalt particles was heated for 4 h at 140–145°C. When the reaction was complete, the mixture was filtered from the catalyst, and the product was isolated by vacuum distillation. Yield 3.1 g (0.016 mol, 67%), bp 160–163°C (10 mmHg),  $n_{\rm D}^{20} = 1.5745$ .

c. A mixture of 5 mL (0.046 mol) of benzylamine and 0.5 g of colloidal nickel particles was heated for 4 h at 130–140°C. The product was isolated by vacuum distillation. Yield 3.5 g (0.018 mol, 78%), bp 160–163°C (10 mmHg),  $n_D^{20} = 1.5745$ .

*N*-Hexylnaphthalen-1-amine (IIIe). A mixture of 10.2 g (0.1 mol) of hexan-1-ol, 6.5 g (0.05 mol) of α-naphthylamine, and 3 g of colloidal nickel particles was heated for 10 h at 160–180°C. The product was isolated by vacuum distillation. Yield 6.9 g (0.031 mol, 61%), bp 210–212°C (10 mmHg). <sup>1</sup>H NMR spectrum, δ, ppm (*J*, Hz): 0.78 t (3H, CH<sub>3</sub>, *J* = 12.6), 1.13 m (6H, CH<sub>2</sub>), 1.37 q (2H, CH<sub>2</sub>, *J* = 20.4), 2.84 t (2H, CH<sub>2</sub>N,

J = 14.0), 3.87 s (1H, NH), 6.28–7.56 m (6H, C<sub>10</sub>H<sub>7</sub>). Found, %: C 84.60; H 9.29; N 6.11. C<sub>16</sub>H<sub>21</sub>N. Calculated, %: C 84.53; H 9.31; N 6.16.

*N*-Hexylquinolin-8-amine (IIIf). A mixture of 10.2 g (0.1 mol) of hexan-1-ol, 7.2 g (0.05 mol) of quinolin-8-amine, and 3 g of nickel nanoparticles was heated for 10 h at 160–180°C. When the reaction was complete, the mixture was filtered from the catalyst, and the product was isolated by vacuum distillation. Yield 6.8 g (0.03 mol, 60%), bp 221–224°C (10 mmHg). <sup>1</sup>H NMR spectrum, δ, ppm (*J*, Hz): 0.86 t (3H, CH<sub>3</sub>, *J* = 13.8), 1.190–1.430 m (6H, CH<sub>2</sub>), 1.64 m (2H, CH<sub>2</sub>), 3.12 t (2H, CH<sub>2</sub>N, *J* = 14.0), 4.33 s (1H, NH), 6.39–8.66 m (6H, C<sub>9</sub>H<sub>6</sub>N). Found, %: C 78.97; H 8.81; N 12.22. C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>. Calculated, %: C 78.90; H 8.83; N 12.27.

*N*-Benzyladamantan-1-ylmethanamine (IIIg). A mixture of 5.4 g (0.05 mol) of benzyl alcohol, 3.3 g (0.02 mol) of adamantan-1-ylmethanamine, and 0.5 g of colloidal nickel was heated for 8 h at 160–180°C. The product was isolated by vacuum distillation. Yield 6.8 g (0.011 mol, 55%), bp 233–236°C (10 mmHg). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm (*J*, Hz): 1.34–2.20 m (16H, C<sub>10</sub>H<sub>15</sub>, NH), 2.56 d (2H, CH<sub>2</sub>, *J* = 14.2), 3.74 d (2H, CH<sub>2</sub>, *J* = 13.9), 6.85–7.30 m (5H, C<sub>6</sub>H<sub>5</sub>). Found, %: C 84.70; H 9.83; N 5.47. C<sub>18</sub>H<sub>25</sub>N. Calculated, %: C 84.65; H 9.87; N 5.48.

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