Reductive alkylation of aniline over copper chromite catalyst: Optimization of reaction condition

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The effect of variables like time, temperature, pressure, and catalyst composition on reductive alkylation of aniline with acetone over copper chromite catalyst has been studied and the reaction mechanism investigated. By optimizing the reaction conditions the yield of desired product has been improved to 93% with nearly 100% selectivity.

Reductive alkylation is a useful reaction in organic synthesis by which an alkyl group can be introduced to nitrogen atom of ammonia, primary or secondary amine with an aldehyde or ketone in the presence of a reducing agent. Copper chromite has been proved as an excellent catalyst for the synthesis of various secondary amines. The aim of the present study is to optimize the reaction conditions and to understand the mechanism of the reaction.

Borsch reported reductive amination of aldehydes and ketones using sodium cyanohydridoborate (NaBH₃CN) in tetrahydrofuran under controlled pH. The reaction of an aldehyde or ketone with ammonia, primary amine or secondary amine at pH 6-8 in the presence of BH₃CN⁻ led to primary, secondary or tertiary amines respectively, by the reductive amination of carbonyl group.

Watanabe reported selective amination of aldehydes and ketones using iron pentacarbonyls. A wide variety of carbonyl compounds was converted to secondary amines by this reaction. Here the ratio of aldehyde to iron pentacarbonyl was 1:1, and reaction time 5-10 h. The reaction was done in alcoholic solution under a carbon monoxide atmosphere. Reductive amination of aldehydes or ketones using NaTeXH in ethyl alcohol at 20°C was reported by Osuki.

Malz reported the synthesis of tertiary amines by reductive alkylation of aliphatic secondary amines with ketones in the presence of hydrogen and palladium, platinum or rhodium on carbon.

The sulphides of rhenium, iron, cobalt, nickel and tungsten have been used as catalysts for the reductive alkylation. The reductive alkylation of amines with carbonyl compounds can be brought about with chemical reducing agents such as selenophenol and borohydrides. The studies on reductive alkylation of ethanolamine and methylamine by carbonyl compounds over copper chromite have been reported. Synthesis of secondary amines by reductive alkylation of aniline with different carbonyl compounds using copper chromite catalyst has been studied to understand the steric effect of carbonyl compounds.

Experimental
Barium oxide promoted copper chromate was prepared by following the procedure reported by Lazier and Mozingo. Composition: CuO (30.5 wt%), Cr₂O₃ (58.5 wt%), BaO (11 wt%), BET surface area 120 m²/g, pore volume 0.28 cc/g, copper content: 24.5%, chromium content: 40%. The phase values (power pattern X-ray diffractogram) of the catalyst was in agreement with values in JCPDS. The catalysts were pretreated by heating in a current of air at 300°C for 4 h followed by passing hydrogen at the same temperature. The reactions were performed in a Teflon lined autoclave of 500 ml capacity. After charging the reactants the autoclave was flushed with nitrogen and then with hydrogen. The effect of the following parameters was studied using fresh catalyst without pre-reduction: time, temperature, pressure, quantity of catalyst etc. One of the parameters was changed, keeping others constant. After the reaction, the catalyst was separated by centrifugation. The quantitative yield of the products was determined by gas chromatography using carbovax column of 5 m length. The secondary amine was purified by distillation and characterised by its PMR and mass spectrum. Since the N-isopropylaniline was the only product found from aniline under the experimental condition, the selectivity is almost 100%.

Results and discussion
Effect of reaction time
To find the effect of reaction time, the reactions were carried out at 15, 30, 60, 120, 180 and 360 min. keeping temperature at 140°C, pressure 50 bar hydrogen, catalyst 4% (w/w) on the basis of the total weight of aniline and acetone. Aniline and acetone were 0.1 mole and 0.3 mole respectively. Yield of
N-isopropylaniline (NIPA) increased from 65.5 to 70.0 mole % when reaction time was changed from 15 to 60 min but afterwards it remained constant at 70.5 even when the reaction time was increased to 360 min.

**Effect of temperature**
Reactions were carried out at 30, 60, 100, 140 and 180 °C, keeping the pressure at 50 bar for 60 min. The aniline to acetone molar ratio was 1:3. The yield of the N-isopropylaniline was 16.5 mole% at 30 °C. It was increased to 70% at 140 °C. The yield was not further enhanced by performing the reaction above 140 °C.

**Effect of pressure**
To understand the effect of pressure the reactions were carried out at 20, 40, 50, 80 and 110 bar hydrogen, at 140 °C for 60 min. Under 20 bar hydrogen pressure the yield of N-isopropylaniline was 22.3 mole%. The yield was increased to 68% at 40 bar hydrogen pressure and 70% at 50 bar pressure. There was not much change in the yield of product at higher pressures like 80 and 110 bar. The optimum pressure for maximum yield was 50 bar.

**Effect of quantity of catalyst**
Barium promoted copper chromite catalyst 2, 4, 6 and 8% (weight percentage on the basis of the total weight of aniline and acetone) were used in the series of reactions of aniline with acetone (1:3) molar ratio at 140 °C and 50 bar pressure for 60 min. Yield of NIPA was 44.0, 70.5, 67.2 and 64.8 mole% respectively which showed that the ideal choice was 4% w/w of the catalyst.

**Effect of the molar ratio of aniline to acetone**
Different ratios viz. 1:1, 1:2, 1:3 (aniline:acetone) were taken for reductive alkylation at 140 °C at 50 bar pressure for 60 min. The quantity of the catalyst in all these experiments was 4%. 1:3 Molar ratio of aniline:acetone was found to be the optimum.

**Effect of pre-reduction of catalyst**
The catalyst was pre-reduced with hydrogen at 300 °C for 4 h. When the reaction between aniline and acetone (1:3 mole ratio) was done at 140 °C for 1 h at 50 bar hydrogen pressure with 4% pre-reduced catalyst, the yield of N-isopropylaniline was increased to 93%. The requirement of pre-reduction of the catalyst was inferred from our earlier studies.

**Mechanism of the reductive alkylation reaction**
The mechanism of the reductive alkylation is straightforward. In the reaction of aniline with acetone, the lone pair of electrons on nitrogen attacks carbonyl carbon, followed by proton exchange and elimination of a molecule of water to give the imine. The imine in the presence of hydrogen and catalyst gets reduced to the secondary amine. Though the secondary amine (Scheme 1) can in principle react further with the ketone to form tertiary amine, this was not observed in any of the reactions studied. Acetone is reduced to isopropyl alcohol in a parallel reaction:

\[
C_6H_5NH_2 + CH_3 - CO - CH_3 \xrightarrow{H_2, \text{catalyst}} \quad \text{C}_6\text{H}_5 - \text{NH} - \text{CH(CH}_3)_2 + \text{H}_2\text{O}
\]

Even though the formation of schiff base can be catalysed, under the present reaction conditions, copper chromite does not seem to have any role in its formation. A 1:1 molar ratio of aniline to acetone when heated in the autoclave at 140 °C under 50 bar nitrogen pressure, with and without added copper chromite gave the schiff base in the same yield (85%). The reaction between aniline and isopropyl alcohol at 140 °C, 50 bar nitrogen pressure without catalyst was performed. No reaction took place. This proved that the direct uncatalysed alkylation of aniline with isopropyl alcohol was not possible. The reaction of aniline with isopropyl alcohol over copper chromite in the presence of hydrogen at 50 bar for 60 min at 140 °C gave N-isopropylaniline (40%). This is most likely due to the initial dehydrogenation of isopropyl alcohol to acetone followed by normal reductive alkylation rather than the direct alkylation of aniline by the alcohol. This view is supported by the observation that the reaction between aniline and isopropyl alcohol at 140 °C for 60 min over copper chromite under 50 bar nitrogen pressure without any added hydrogen did not produce secondary amine.

**Mechanism of hydrogenation of schiff base**
The mechanism of the hydrogenation of a variety of double bonds by copper chromite and related catalysts have been studied by Hubaut et al. They have concluded that coordinately unsaturated cuprous ions on the surface are the active centres. Cuprous hydride formed by the dissociate adsorption of hydrogen has been proposed as the active species. These proposals have been adopted to give the model in Scheme 2 for the reduction of schiff base. The strong inhibition of acetone hydrogenation by the nitrogenous molecules observed in the present study is readily understood on the basis of this model. The basic amines compete with the carbonyl compound for the coordinately unsaturated copper sites and prevent their adsorption and reaction.
The repeated use of the same catalyst for different cycle of reactions showed that the catalyst requires induction period to get maximum activity. So the catalyst was preactivated by heating in a current of air at 300°C followed by passing hydrogen at the same temperature for 4 h. The reaction using prereduced catalyst gave an yield of 93% of N-isopropylaniline.

\[ \text{C}_6\text{H}_5 - \text{N} = \text{C(CH}_3)_2 \xrightarrow{\text{H}_2, \text{catalyst}} \text{C}_6\text{H}_5 - \text{NH} - \text{CH(CH}_3)_2 \]

The optimum reaction conditions for the reductive alkylation of aniline over copper chromite: time, temperature, pressure and weight percentage of the catalyst are 60 min, 140°C, 50 bar and 4% respectively. As the quantity of acetone increases the yield of N-isopropylaniline also increases. The usage of excess amount of acetone can be avoided by doing the reaction stepwise, that is by first synthesising imine in nitrogen pressure, followed by continuing the reaction in the presence of hydrogen. By using preactivated catalyst under the above optimum reaction conditions the yield of N-isopropylaniline was 93%. The analysis of reaction mixture showed that selectivity is nearly 100%.

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References