SELECTIVE CONVERSION OF PRIMARY AMINES INTO N,N-DIMETHYL-ALKYL- OR N,N-DIALKYLMETHYL-AMINES WITH METHANOL AND $RuCl_2(Ph_3P)_3$

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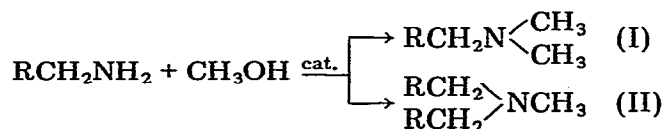*Istituto Chimico "G. Ciamician" Università di Bologna, Via Selmi 2, Bologna (Italy)*

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Summary

N,N-dimethylalkyl- or N,N-dialkylmethyl-amines are selectively obtained from the reaction between aliphatic amines and methanol at 180°C for 7 h in the presence of $RuCl_2(Ph_3P)_3$ catalyst.

The alkylation of primary and secondary amines with alcohols promoted by $RhH(Ph_3P)_4$ was recently reported by Grigg et al. [1], and a method of obtaining N-alkylanilines by alkylation of aniline with alcohols in the presence of $RuCl_2(Ph_3P)_3$ catalyst was described by Watanabe [2]. In connection with our interest in the $RuCl_2(Ph_3P)_3$ catalyzed synthesis of secondary [3], tertiary, and heterocyclic amines [4,5], we now report another application of this catalyst in amine synthesis.

We have found that the reaction between methanol and primary aliphatic amines bearing an α-hydrogen atom gives two different products, depending on the conditions employed. By an appropriate choice of the amount of catalyst and the ratio of reactants, it is possible to obtain N,N-dimethylalkylamines (I) or N,N-dialkylmethylamines (II) selectively, as shown in the following Scheme:

$$RCH_2NH_2 + CH_3OH \xrightarrow{cat.} \begin{cases} RCH_2N{<}^{CH_3}_{CH_3} \quad (I) \\ {}^{RCH_2}_{RCH_2}{>}NCH_3 \quad (II) \end{cases}$$

The amine and methanol are allowed to react at 180°C for 7 h in a sealed glass tube in the presence of homogeneous catalyst $RuCl_2(Ph_3P)_3$.

A preliminary experiment carried out on benzylamine showed that the reaction does not occur with a satisfactory yield at the reflux temperature. Thus, using 6 mol% of catalyst and a 2.5 MeOH/benzylamine molar ratio, N,N-dibenzylmethylamine was recovered in 51% yield after 7 h, along with dibenzylamine (7%) and tribenzylamine (41%).

Representative results are summarized in Table 1 and, some features of interest can be discussed. When the methanol was in large excess (15—30 molar ratio of MeOH/amine) and 1—1.3 mol% of catalyst (based on the amine) was used, N,N-dimethylalkylamine (I) was obtained in good yield (86—98%); the monomethylated product ($RNHCH_3$) was observed, in poor yield, only in the case of n-butyl and n-benzylamine. In contrast, use of a 2.5—5 molar ratio of MeOH/amine and 4—6.5 mol% of catalyst gave N,N-dialkylmethylamine (II) as the main product (72—93%); except the case of cyclohexylamine, symmetrical secondary (R_2NH) and tertiary (R_3N) amines were generally found in small amounts under these conditions. These by-products practically disappear if a larger amount of methanol is used (see n-butylamine) or the reaction time is prolonged (see n-dodecylamine).

From the results it appears that an increase in the length of the carbon chain of the starting primary amine leads to an increase in the catalyst percentage (from 4 to 6.5 mol%) required to give good yields of the corresponding N,N-dialkylmethylamine (II); this is presumably due to the increased bulk of the alkyl group linked to the nitrogen atom, as noted previously in the synthesis of symmetrical secondary and tertiary amine [3,4]. The results obtained with cyclohexylamine confirm that the reaction is sensitive to the steric hindrance in the amine; thus, while N,N-dimethylcyclohexylamine was obtained in 95% yield, N,N-dicyclohexylmethylamine was isolated in poor yield along with a moderate amount of dicyclohexylamine (see Table 1).

TABLE 1

SELECTIVE CONVERSION OF PRIMARY ALKYLAMINES INTO DIMETHYLALKYL- OR DIALKYLMETHYL-AMINES BY REACTION OF MeOH IN THE PRESENCE OF $RuCl_2(Ph_3P)_3$

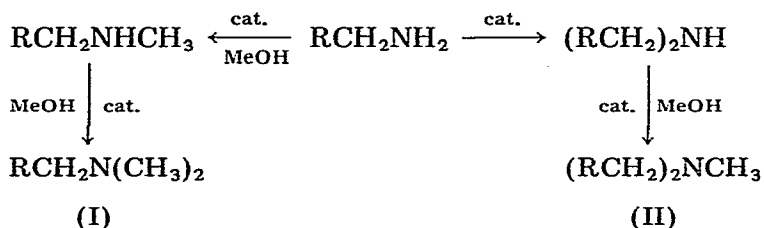| Primary amine R—NH$_2$ R—	Reaction conditions [a]		Products (% yield) [b]		
	Mol% cat. [c]	Mol. ratio MeOH/amine	RN(CH$_3$)$_2$	R$_2$NCH$_3$	Other amines
n-Butyl	1	15	75	—	20 [d]
	1.3	15	86 (80)	—	15 [d]
	4	2.5	18	65	17 [e]
	4	5	19	75 (65)	—
n-Hexyl	1	15	82	18	—
	1.3	15	94 (88)	—	—
	4	2.5	7	72 (60)	15 [e]
n-Octyl	1	15	98 (90)	—	—
	6	2.5	12	86 (75)	—
n-Dodecyl	1	15	94 (86)	—	—
	6	2.5	15	65	16 [e]
	6.5 [f]	2.5	—	93 (80)	—
Cyclohexyl	1.3	15	95 (85)	—	—
	6.5 [f]	2.5	20	25	53 [g]
Benzyl	1	15	26	39	35 [d]
	1.3	30	95 (90)	—	—
	3	2.5	47	49	—
	6	2.5	16	81 (70)	—

[a] Reaction performed at 180°C for 7 h unless stated otherwise. [b] Determined by GLC analysis; in parentheses the yields of isolated products are reported. [c] Based on the amine used. [d] RNHCH$_3$. [e] R$_2$NH plus R$_3$N. [f] Reaction time 12 h. [g] R$_2$NH.

With a low percentage of the catalyst and in the presence of a large excess of methanol, no symmetrical secondary (R_2NH) and tertiary (R_3N) amines were ever found, while monomethylalkylamine ($RNHCH_3$) was detected in the reactions with n-butylamine (20%) and benzylamine (35%). In contrast when the reaction was carried out with a low MeOH/amine molar ratio and a higher percentage of the catalyst, R_2NH and R_3N were generally present, whilst $RNHCH_3$ was never detected.

In aid in elucidating the reaction path leading to dialkylmethylamine (II), it is useful to consider the results obtained in an additional experiment carried out on n-hexylamine using a 2.5 MeOH/hexylamine molar ratio and in the presence of 4 mol% of catalyst. Analysis of the products after 3 h showed *N,N*-dihexylmethyl- (28%) and dihexyl-amine (46%) to be present along with trihexyl- (14%) and *N*-methylhexyl-amine (10%); after 7 h the yield of *N,N*-dihexylmethylamine reached 72% at the expense of dihexylamine, which practically disappeared.

A possible explanation for the results is that the reactions involve the intermediates, $RNHCH_3$ and R_2NH in the formation of $RN(CH_3)_2$ and R_2NCH_3, respectively. However, in the path leading to R_2NCH_3 one cannot rule out (especially with a starting amine containing a small alkyl group) the presence of the intermediate $RNHCH_3$, which can be successively converted into R_2NCH_3, as previously observed under similar conditions [5].

The results, considered along with the mechanism suggested by Grigg [1] and Watanabe [2] for amine alkylation, lead us to suggest the following possible reaction routes:

$$RCH_2NHCH_3 \xleftarrow[\text{MeOH}]{\text{cat.}} RCH_2NH_2 \xrightarrow{\text{cat.}} (RCH_2)_2NH$$

$$\text{MeOH} \Big\downarrow \text{cat.} \qquad\qquad\qquad\qquad\qquad \text{cat.} \Big\downarrow \text{MeOH}$$

$$RCH_2N(CH_3)_2 \qquad\qquad\qquad\qquad\qquad (RCH_2)_2NCH_3$$

$$\text{(I)} \qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{(II)}$$

General procedure

A mixture of the primary alkylamine (6 mmol) and methanol (15—180 mmol) was sealed in a glass tube in the presence of $RuCl_2(Ph_3P)_3$ (0.06—0.39 mmol) and kept for 7 h at 180°C. The products were analyzed in GLC by comparison with authentic samples, and the yields were determined by use of an internal standard. The products derived from n-butyl-, n-dodecyl- and cyclohexyl-amine were identified by MS and ^{1}H NMR analysis.

The best results achieved for each substrate were confirmed for reactions involving a two-fold increase in the quantities of reactants. The purity of the products, isolated by distillation ($RN(CH_3)_2$) or by elution on alumina (R_2NCH_3), was checked by GLC using the following columns: 2 m × 2 mm, SE52 (5%) on Chromosorb W (for *N,N*-dimethylbenzylamine and *N,N*-dibenzylmethylamine) and 2 m × 2 mm, Versamid 900 and NaOH (0.5%) on Chromosorb G (for the other amines).

References

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