Tetrahedron Letters,Vol.23,No.2,pp 229-232,1982 0040-4039/82/020229-04$03.00/0
Printed in Great Britain

RUTHENIUM CATALYZED SYNTHESIS OF SECONDARY OR TERTIARY AMINES FROM AMINES AND ALCOHOLS

Shun-Ichi Murahashi*, Kaoru Kondo, and Toshiyuki Hakata

Department of Chemistry, Faculty of Engineering Science, Osaka
University, Machikaneyama, Toyonaka, Osaka, Japan 560.

Summary: Unsymmetrical secondary and tertiary amines are prepared by the ruthenium catalyzed reaction of alcohols with amines, which provides highly efficient method for synthesis of cyclic amines.

Catalytic preparation of unsymmetrical amines are important in view of synthetic means and industrial process.[1] The reaction of alcohols with amines are interesting in comparison with the reductive alkylation of amines with aldehydes.[2] Using palladium catalysts, reactive benzylic and allylic alcohols are readily activated and react with amines respectively to give unsymmetrical amines.[3] We now wish to report an efficient process for synthesis of unsymmetrical secondary and tertiary amines from the reaction of aliphatic alcohols with amines, using homogeneous $RuH_2(PPh_3)_4$ catalyst, as depicted in eq. 1.[4] The reaction is particularly convenient for synthesis of cyclic nitrogen compounds.

$$R^1R^2CHOH \quad + \quad R^3R^4NH \xrightarrow{RuH_2(PPh_3)_4} R^1R^2CHNR^3R^4 \qquad (1)$$

Recently $RuCl_2(PPh_3)_3$ and $RhH(PPh_3)_4$ catalysts were used for the activation of aliphatic alcohols.[5,6,7] The most crucial point for these reactions is the exclusive activation of alcohols with catalysts. $RuCl_2(PPh_3)_3$ is, for example, a good catalyst for the activation of both alcohols and amines, resulting in the competitive formation of secondary amines[8] by amine exchange reactions.[1] Therefore, $RuCl_2(PPh_3)_3$ is utilized for the alkylation of less reactive arylamines.[6] Alternatively, the alkylation reaction by $RhH(PPh_3)_4$ catalyst has been carried out in the presence of large excess of alcohols.[7]

It is found that $RuH_2(PPh_3)_4$ is highly selective for the activation of alcohols. When an equimolar mixture of an alcohol and an amine was allowed to react at 155°,[9] an unsymmetrical amine is formed highly selectively. The representative examples of the present reaction were summarized in Table 1.

General procedure is as follows. Into a 10 mL stainless steel autoclave, fitted with a magnetic stirring bar was placed 0.144 g of $RuH_2(PPh_3)_4$ (0.125 mmol). The autoclave was evacuated and fitted with argon alternately on vacuum line. An alcohol (5.0 mmol) and an amine (5.0 mmol) were introduced with cylinge technique, and the mixture was allowed to react with stirring at 155-180° for 6 to 24 hr. After cooling, the reaction mixture was subjected to bulb-to-bulb distillation.

Intramolecular versions of the present reaction provide highly efficient methods for synthesis of cyclic amines. Treatment of 4-amino-1-butanol with $RuH_2(PPh_3)_4$ catalyst gave pyrrolidine in 79% yield. Although tertiary cyclic amines (4) can be prepared by either the reaction of diols (3) with primary amines or that of aminoalcohols (1) with alcohols, the former reaction is more convenient, since the yield is higher as is apparent from the results shown in Table 2, and the starting diol is more accessible. Noticeable is the high yield of the seven-membered N-hexylhexamethyleneimine derived from 1,6-hexanediol. This is due to the template effect of ruthenium to bidentate diols.

Further applications of the synthesis of cyclic amines confirm the efficiency of the present reaction. Tetrahydroisoquinolines can be readily prepared. Thus, treatment of 2-(2-hydroxyethyl)benzyl alcohol (5), which are readily prepared from benzyl alcohol,[10] with benzylamine gave N-benzyltetrahydroisoquinoline (6) in 62% isolated yield (preparative TLC), while the treatment of 5 with 3,4-dimethoxyphenylethylamine gave tetrahydroisoquinoline (7) in 42% isolated yield.

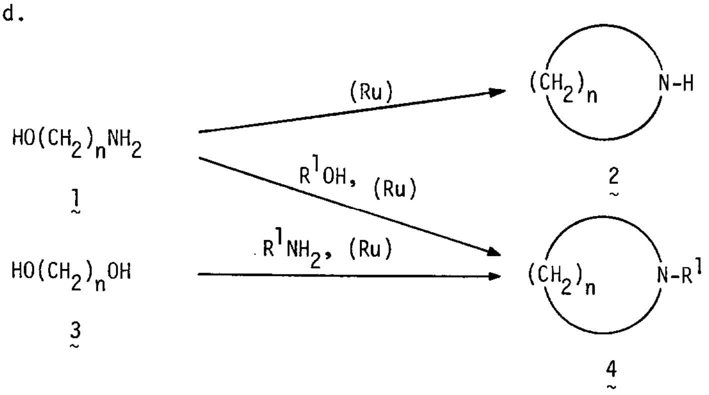
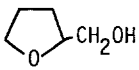
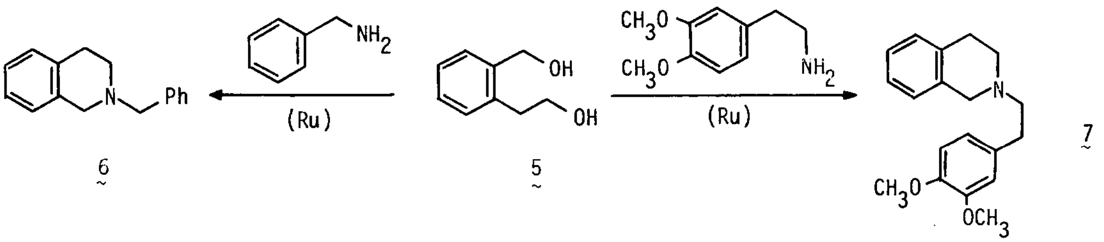


Table 1. Ruthenium Catalyzed Reaction of Alcohols with Amines

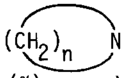
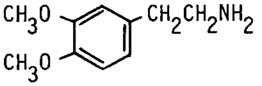
Alcohol	Amine	Temp.(°C)	Time(hr)	Secondary Amine [a] Conv.(%)	Yield(%)
$C_7H_{15}OH$	$C_8H_{17}NH_2$	180	6	94	98
$C_{10}H_{21}OH$	$C_8H_{17}NH_2$	180	6	70	74
	$C_8H_{17}NH_2$	180	6	84	75
$CH_3CH_2CH(CH_3)OH$	$C_6H_{13}NH_2$	160	24	88	52

[a] Determined by glc analysis using internal standards.

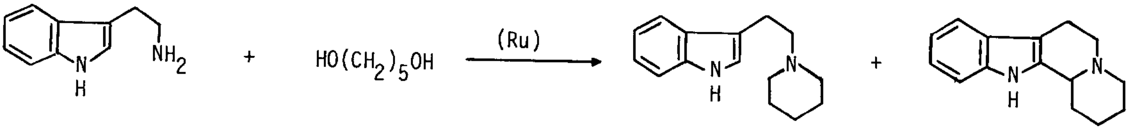


Moreover, the cyclization reaction can be utilized for construction of indole derivatives. Thus, treatment of 1,5-pentanediol with tryptamine gave N-[2-(3-indolyl)ethyl]piperidine[11] (8) (33%) along with 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine[9] (9)(6 %).

Table 2. Ruthenium Catalyzed Reaction of Diols and Aminoalcohols

HO(CH$_2$)$_n$X	R-Y	Condition[a]	Time(hr)	 (CH$_2$)$_n$ N-R [b] Conv.(%)	Yield(%)
HO(CH$_2$)$_4$NH$_2$	-	A	24	100	79(R=H)
HO(CH$_2$)$_4$NH$_2$	C$_6$H$_{13}$OH	B	24	55	58
HO(CH$_2$)$_4$OH	C$_6$H$_{13}$NH$_2$	C	20	70	40[c]
HO(CH$_2$)$_5$NH$_2$	-	A	24	71	89(R=H)
HO(CH$_2$)$_5$NH$_2$	C$_6$H$_{13}$OH	B	24	50	80
HO(CH$_2$)$_5$OH	C$_6$H$_{13}$NH$_2$	C	4	58	83
HO(CH$_2$)$_5$OH	 CH$_3$O, CH$_3$O, CH$_2$CH$_2$NH$_2$	C	24	88	92
HO(CH$_2$)$_6$NH$_2$	-	A	18	100	41(R=H)
HO(CH$_2$)$_6$NH$_2$	C$_6$H$_{13}$OH	B	6	75	21[d]
HO(CH$_2$)$_6$OH	C$_6$H$_{13}$NH$_2$	C	24	100	87

[a] (condition A), HO(CH$_2$)$_n$NH$_2$ (5 mmol), (condition B) a mixture of HO(CH$_2$)$_n$NH$_2$ (5 mmol) and ROH (5 mmol), (condition C)a mixture of HO(CH$_2$)$_n$OH (5 mmol) and RNH$_2$ (5 mmol) was allowed to react in the presence of 2.5 mol% of RuH$_2$(PPh$_3$)$_4$ catalyst at 155° under argon. [b] Determined by glc analysis using internal standards. [c] N-Hexylpyrrole (20%) was obtained. [d] Hexamethyleneimine (53%) was obtained.



8 9

The reaction can be rationalized by assuming equations (2)-(4), where (Ru) stands for the active low valent ruthenium catalyst. The key intermediate is the iminium ion complex.[12]

$$R^1R^2CHOH + (Ru) \rightleftharpoons (R^1R^2C{=}O)(Ru)(H_2) \qquad (2)$$

$$(R^1R^2C{=}O)(Ru)(H_2) + R^3R^4NH \rightleftharpoons (R^1R^2C{=}\overset{+}{N}R^3R^4)(Ru)(\overset{-}{H}) + H_2O \qquad (3)$$

$$(R^1R^2C{=}\overset{+}{N}R^3R^4)(Ru)(\overset{-}{H}) \rightleftharpoons R^1R^2CHNR^3R^4 + (Ru) \qquad (4)$$

We gratefully acknowledge the award of Grants from Takeda Science Foundation. We wish to thank professor Shin-ichiro Sakai for the generous gifts of 8 and 9.

References and Notes

1) N. Yoshimura, I. Moritani, T. Shimamura, and S.-I. Murahashi, J. Am. Chem. Soc., 95, 3038 (1973).
2) W. S. Eberson, Org. Reactions, 4, 174 (1948).
3) S.-I. Murahashi, T. Shimamura, and I. Moritani, Chem. Commun., 931 (1974).
4) S.-I. Murahashi, T. Hakata, and K.Kondo, 41st Annual Meeting of the Chemical Society of Japan, (Osaka), April 1, 1980, Abstract II, 845 (3026).
5) Y. Sasson and J. Blum, Chem. Commun., 309 (1974).
6) Y. Watanabe, Y. Tsuji, Y. Ohsugi, Tetrahedron Lett., 2667 (1981).
7) R. Grigg, T. R. B. Mitchell, S. Sutthiyaiyakit, N. Tongpenyai, Chem. Commun., 611 (1981).
8) The reaction of butanol (10 mmol) with hexylamine (10 mmol) in the presence of 2.5 mol% of $RuCl_2(PPh_3)_3$ at 155° for 24 hr gave N-butylhexylamine (1.1 mmol) and dihexylamine (1.0 mmol).
9) The hydrogen transfer step requires higher reaction temperature than 155°. At lower temperature, considerable amount of the corresponding Schiff base is formed. Thus, the reaction of hexylamine (10 mmol) with butanol (10 mmol) in the presence of 2.5 mol% of $RuH_2(PPh_3)_4$ at 110° for 24 hr gave N-butylhexylamine (0.5 mmol) and N-butylidenehexylamine (3.4 mmol) along with butanol (5.9 mmol) and hexylamine (6.2 mmol).
10) Direct lithiation of benzyl alcohol, followed by treatment with ethylene oxide gave 5 in 50 % isolated yield (bp. 150°/ 5 mmHg).
11) G. W. Gribble, J. Org. Chem., 37, 1833 (1972).
12) S.-I. Murahashi, T. Hirano, and T. Yano, J. Am. Chem. Soc., 100, 348 (1978); S.-I. Murahashi, T. Watanabe, ibid., 101, 7429 (1979).

(Received in Japan 29 September 1981)