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Ruthenium Complex-Catalyzed N-Heterocyclization. Syntheses of *N*-Substituted Pyrroles and Pyrrolidines from 1,4-Diols and Primary Amines

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Synopsis. 2-Butyne-1,4-diol reacts with aliphatic amines in the presence of a catalytic amount of $[RuCl_2(PPh_3)_3]$ at 150 °C to give *N*-alkylpyrroles in good yields. 1,4-Butanediol reacts with aromatic or aliphatic amines to give *N*-substituted pyrrolidines in excellent yields; $[RuCl_2(PPh_3)_3]$ and $[RuCl_3 \cdot nH_2O\text{-}3PBu_3]$ are the best catalysts for aromatic and aliphatic amines, respectively. The reaction of 2-butene-1,4-diol with alkyl amines gives a 1:1 mixture of *N*-substituted pyrroles and pyrrolidines in high yield.

Pyrroles and pyrrolidines, well-known and very important compounds in organic syntheses and in many other fields, are prepared by various methods[1] including inter- and intramolecular cyclization of tetramethylene dibromides,[2] 4-halo-1-butanamines,[3] α-amino ketones,[4] α-halo ketones,[5] and 1,4-diketones.[6] Recently, transition metal-catalyzed synthetic methods of pyrrole derivatives have been developed.[7,8] In the course of our studies on the ruthenium complex-catalyzed *N*-heterocyclization using alcohols[9] we found a novel synthetic method of *N*-substituted pyrroles and pyrrolidines from readily availabe 1,4-diols and primary amines.

Experimental

General Reaction Procedure. All boiling points and melting points were uncorrected. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 100 and 25.05 MHz, respectively, with a JEOL JNM FX-100 spectrometer. Elemental analyses were performed at the Microanalytical Center of Kyoto University. The GLC analyses were made using Shimadzu GC-4CM with a column (3 mm×3 m) packed with Apiezon Grease L (10%) on Neopack 1A, 60—80 mesh. Gel-permeation chromatograms (GPC) were recorded on a Waters ALC/GPC 244 system equipped with a Shodex GPC H-2002 column. Typical reaction conditions were as follows. A stainless-steel reactor (50 ml Taiatsu Glass Industry, TVS-1 type) containing a glass liner was used. Under an argon stream, dioxane (5 ml), amine (2 mmol), 2-butyne-1,4-diol (3 mmol), and $[RuCl_2(PPh_3)_3]$ (0.02 mmol, 1 mol% based on the amines used) were added into the glass liner. After the reactor was flushed with argon (10 atm) four times, the reactor was held at 150 °C for 5 h. The products were isolated by vacuum distillation or medium-pressure column chromatography (hexane or benzene–aluminum oxide 90, Merck, No. 1076). Spectral data of unreported compounds are as follows.

(±)-1-(2-Ethylhexyl)pyrrole: Colorless oil; Kugelrohr pot temp. 60 °C (0.04 mmHg[†]); ^1H NMR δ=0.80—0.93 (6H, m, $2CH_3$), 1.14—1.34 (8H, m, $4CH_2$), 1.48—1.86 (1H, m, CH), 3.71 (2H, d, CH_2), 6.09 (2H, t), 6.60 (2H, t); ^{13}C NMR δ=10.6 (q, CH_3), 14.0 (q, CH_3), 23.0 (m, CH_2), 23.8 (m, CH_2), 28.7 (m, CH_2), 30.6 (m, CH_2), 41.3 (d, CH), 53.1 (t, CH_2), 107.6 (d), 120.9 (d). Found:C, 80.13; H, 11.93; N, 7.63%. Calcd for $C_{14}H_{21}N$: C, 80.38; H, 11.80; N, 7.63%.

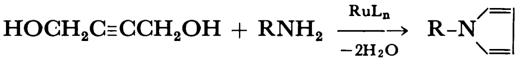
1-(5-Indanyl)pyrrolidine: White crystals; mp 42—44 °C; bp 112—118 °C (0.60 mmHg); ^1H NMR δ=1.86—2.16 (6H, m, $3CH_2$), 2.73—2.92 (4H, m, $2CH_2$), 3.15—3.28 (4H, m, $2N\text{-}CH_2$), 6.36 (1H, dd, J=7.6 and 2.6 Hz, Ph), 6.46 (1H, s, Ph), 7.05 (1H, d, Ph); ^{13}C NMR δ=25.4 (t, $2CH_2$), 25.8 (t, CH_2), 31.9 (t, CH_2), 33.3 (t, CH_2), 48.0 (t, $2N\text{-}CH_2$), 107.8 (d), 110.0 (d), 124.6 (d), 130.9 (s), 145.1 (s), 147.1 (s). Found: C, 83.16; H, 9.26; N, 7.21%. Calcd for $C_{13}H_{17}N$: 83.37; H, 9.15; N, 7.48%.

1-(3-Trifluoromethylphenyl)pyrrolidine: Colorless oil; bp 60—62 °C (0.27 mmHg); ^1H NMR δ=1.65—1.78 (4H, m, $2CH_2$), 2.90—3.03 (4H, m, $2N\text{-}CH_2$), 6.31—7.14 (5H, m, Ph); ^{13}C NMR δ=25.5 (m, $2CH_2$), 47.6 (t, $2N\text{-}CH_2$), 107.9 (d; $J_{F\text{-}C\text{-}C\text{-}C}$=3.66 Hz), 111.5 (d; $J_{F\text{-}C\text{-}C\text{-}C}$=4.88 Hz), 114.6 (d), 124.7 (q, CF_3; $J_{F\text{-}C}$=272.3 Hz), 129.4 (d), 131.4 (q, $J_{F\text{-}C\text{-}C}$=31.7 Hz), 147.9 (s). Found: C, 61.59; H, 5.61; N, 6.55; F, 26.20%. Calcd for $C_{11}H_{12}NF_3$: C, 61.39; H, 5.62; N, 6.51; F, 26.48%.

1-(3,4-Methylenedioxyphenyl)pyrrolidine: White crystals; mp 70 °C; bp 110 °C (0.30 mmHg); ^1H NMR δ=1.91—2.04 (4H, m, $2CH_2$), 3.15—3.28 (m, 4H, $2N\text{—}CH_2$), 5.84 (s, 2H, $O\text{-}CH_2\text{-}O$), 5.98 (dd, 1H, *J*=8.8 and 2.6 Hz, Ph), 6.23 (1H, d, *J*=2.6 Hz, Ph), 6.71 (1H, d, *J*=8.8 Hz, Ph); ^{13}C NMR δ=25.3 (t, $2CH_2$), 48.3 (t, $2N\text{-}CH_2$), 94.4 (d), 100.3 (t, $O\text{-}CH_2\text{-}O$), 103.0 (d), 108.6 (d), 138.1 (s), 144.4 (s), 148.2 (s). Found: C, 68.79; H, 6.87; N, 7.17; O, 16.82%. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32; O, 16.73%.

Results and Discussion

Synthesis of *N*-Substituted Pyrroles from 2-Butyne-1,4-diol and Amines. The reaction between 2-butyne-1,4-diol (**1**) and aliphatic primary amines **4** at 150 °C in dioxane in the presence of catalytic amounts of a ruthenium complex afforded *N*-substituted pyrroles **5** (Eq. 1, Table 1). When $[RuCl_2(PPh_3)_3]$ was used as a catalyst, the reaction of octylamine with 2-butyne-1,4-diol gave 1-octylpyrrole in 63% yield. The catalytic activity was little affected by the phosphorus ligands; $[RuCl_2(PPh_3)_3]$, $[RuCl_3 \cdot nH_2O\text{-}3PBu_3]$, and $[RuCl_3 \cdot nH_2O]$ showed high catalytic activity (63, 52, and 57% yield of **5**, respectively) and other ruthenium complexes such as $[RuHCl(CO)(PPh_3)_3]$ and $[RuBr_2(PPh_3)_3]$ were also effective (58 and 53% yield of **5**, respectively). Addition of bis(diphenylphosphino)ethane (dppe) as a bidentate phosphorus ligand or a bulky PCy_3 suppressed the catalytic activity considerably (4 and 1% yield, respectively). No satisfactory results were obtained in case of aromatic amines. When 2-butyne-1,4-diol (**1**) was treated with a

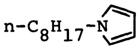
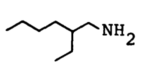
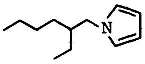
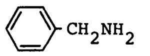
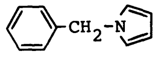
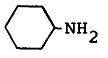
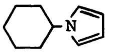
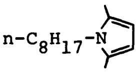


$$HOCH_2C{\equiv}CCH_2OH + RNH_2 \xrightarrow[-2H_2O]{RuL_n} \text{R-N} \qquad (1)$$

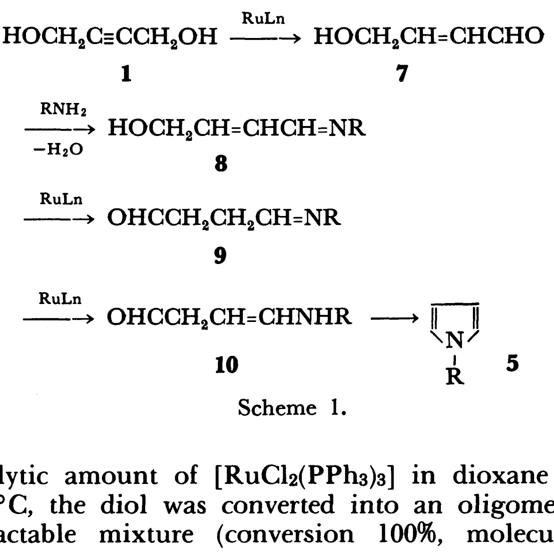
1 **4** **5**

[†] 1 mmHg=133.322 Pa.

Table 1. N-Substituted Pyrrole Synthesis[a)]

Run	Amine	1,4-Diol	Product	Yield[c)]/%
1	n-$C_8H_{17}NH_2$	$HOCH_2C{\equiv}CCH_2OH$		63 (59)
2		$HOCH_2C{\equiv}CCH_2OH$		(49)
3		$HOCH_2C{\equiv}CCH_2OH$		49 (24)
4		$HOCH_2C{\equiv}CCH_2OH$		(27)
5[b)]	n-$C_8H_{17}NH_2$	$HO(CH_3)CHC{\equiv}CCH(CH_3)OH$		(47)

a) Amine (2.0 mmol), 1,4-diol (3.0 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol), dioxane (5 mL), at 150 °C for 5 h. b) Amine (10 mmol), 1,4-diol (15 mmol), $RuCl_2(PPh_3)_3$ (0.10 mmol). c) Determined by GLC based on the amine and figures in the parentheses are isolated yields.

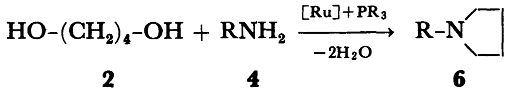


Scheme 1.

catalytic amount of $[RuCl_2(PPh_3)_3]$ in dioxane at 150 °C, the diol was converted into an oligomeric intractable mixture (conversion 100%, molecular weight 200—1000 by GPC). The ruthenium complexes are well-known catalysts for the isomerization of olefins[10)] and of allyl alcohol to aldehyde.[11)] Therefore, we postulate a reaction route (shown in Scheme 1) including the isomerization of 2-butyne-1,4-diol (**1**) to γ-hydroxy-α,β-unsaturated aldehyde (**7**),[12)] which reacts with amines **3** to give imine intermediates **8**. An allylic alcohol moiety of **8** isomerizes again to an imino aldehyde species **9**, which subsequently gives **10** via imine–enamine isomerization.[13)] N-Substituted pyrroles **5** would be produced by intramolecular cyclization of **10**.

The N-heterocyclization to the pyrroles seems to compete with the oligomerization of **7**, since α,β-unsaturated aldehydes are reported to be easy to oligomerize.[14)] When more basic aliphatic amines are employed as the substrate, most of **7** is trapped with them to give **8**. On the other hand, with less basic aromatic amines, a considerable amount of **7** is consumed by the oligomerization.

Synthesis of N-Substituted Pyrrolidines from 1,4-Butanediol and Amines. The reaction of 1,4-butanediol (**2**) with primary amines **4** in the presence of a catalytic amount of a ruthenium complex to give N-substituted pyrrolidines **6** in excellent yields (Eq. 2, Table 2). The reaction is drastically affected by the nature of the phosphorus ligand employed, and the most suitable phosphorus ligand depends on the basicity of the amine.[15)]

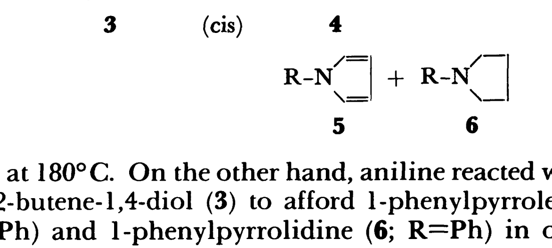


(2)

Dichlorotris(triphenylphosphine)ruthenium ($[RuCl_2(PPh_3)_3]$) was the most effective catalyst for less basic amines (Runs 6—11), while $[RuCl_3 \cdot nH_2O\text{-}3PBu_3]$ was highly effective for the amines with high basicity (Runs 12—15). Methoxy, chloro, trifluoromethyl, and methylenedioxy groups did not affect the catalysis appreciably (Runs 7, 9—11). Amines containing an N-hetero ring such as 3-picolylamine and tryptamine also afforded the desired N-substituted pyrrolidines in good yields (Runs 14 and 15).

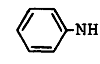
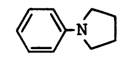
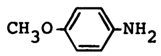
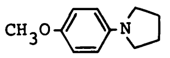
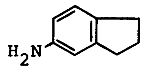
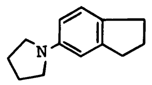
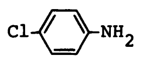
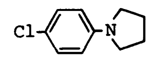
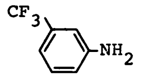
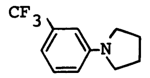
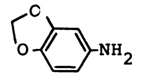
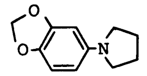
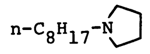
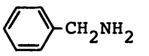
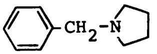
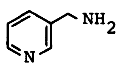
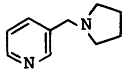
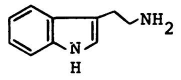
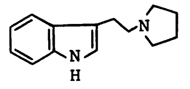
The reaction would proceed via a route analogous to that proposed in the previous paper.[9)]

The Reaction of *cis*-2-Butene-1,4-diol with Amines. *cis*-2-Butene-1,4-diol (**3**) reacted with octylamine in the presence of 1.0 mol% of $[RuCl_3 \cdot nH_2O\text{-}3PBu_3]$ to afford a mixture of 1-octylpyrrole (**5**; $R=n$-C_8H_{17}) and 1-octylpyrrolidine (**6**; $R=n$-$C_{18}H_{17}$) in 1 : 1 molar ratio (Eq. 3). Their combined yields were 69% at 150 °C and 73% at 180°C. On the other hand, aniline reacted with cis-2-butene-1,4-diol (**3**) to afford 1-phenylpyrrole (**5**; R=Ph) and 1-phenylpyrrolidine (**6**; R=Ph) in only 4—9% yields (**5**:**6**=1:9).



(3)

Table 2. *N*-Substituted Pyrrolidine Synthesis[a]

Run	Amine	Catalyst[c]	Temp/°C	Time/h	Product	Yield[d]/%
6		A	140	5		85 (80)
7		A	140	5		(73)
8		A	140	5		(72)
9		A	160	20		(78)
10		A	180	10		(81)
11[b]		A	180	20		(45)
12	n-$C_8H_{17}NH_2$	B	180	5		91 (91)
13		B	180	5		(91)
14[b]		B	180	20		(61)
15[b]		B	180	24		(59)

a) Amine (10 mmol), 1,4-butanediol (15 mmol), catalyst (1.0 mol% based on the amine), dioxane (5 mL). b) Dioxane (15 mL). c) A: $RuCl_2(PPh_3)_3$; B: $RuCl_3 \cdot nH_2O + 3PBu_3$. d) Determined by GLC based on the amine and figures in the parentheses are isolated yields.

In this case, a mixture of **10** and 4-aminobutanal would be formed by the intermolecular hydrogen transfer followed by cyclization to give pyrroles and pyrrolidines, respectively.

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