Journal of Organometallic Chemistry, 407 (1991) 97–105
Elsevier Sequoia S.A., Lausanne
JOM 21596

Ruthenium catalyzed reactions of ethylene glycol with primary amines: steric factors and selectivity control

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(Received September 24th, 1990)

Abstract

The selectivity of reactions of ethylene glycol with primary amines in the presence of $RuCl_2(PPh_3)_3$ at 120°C is highly dependent on the steric nature of the amine. Selectivity to di-amination is favored by smaller alkyl groups on the amine while large amines cleanly yield ethanolamines. This contrasts with the results obtained with secondary amines at this temperature, in which ruthenium-triphenylphosphine catalyst systems always favor mono-amination. In the case of sec-butyl amine, where almost equal amounts of mono- and di-aminated product are obtained, the selectivity can be shifted to mono-amination by the addition of excess triphenylphosphine. The steric effects seen in these reactions are consistent with standard steric parameters available from the literature.

Introduction

An argument often made in favor of homogeneous catalysts is that these types of catalysts often allow reactions to occur at lower temperatures and with higher selectivity than heterogeneous catalysts. In addition, the ability to vary the ligand environment gives homogeneous catalysis an advantage that is sometimes remarkable in its subtleness and which affords a high degree of control [1].

We [2] and others [3–5] have recently reported the ease with which diols can be made to react with amines in the presence of homogeneous transition metal catalysts. In particular, the use of ligands to drastically alter the selectivity of these reactions is noteworthy. We now report further evidence of the remarkable environment of the ruthenium–triphenylphosphine catalyst system, which allows great control of the reaction of ethylene glycol with primary amines.

Experimental

Materials

Ethylene glycol (Aldrich, 99+%) was degassed by heating to 50°C under vacuum (10^{-2} torr) for 3 h. Amines were distilled from BaO under N_2. Methylamine was an exception in that it was dispensed as a gas from a lecture bottle without further purification. The catalyst precursors $RuCl_2(PPh_3)_3$ and $Ru_3(CO)_{12}$

were purchased from Strem and Alfa chemical companies, and little difference in reactivity was noted between material supplied by the two vendors. Unless otherwise stated, product ethanolamines (**1**), diamines (**2**), and piperazines (**3**) were obtained from Aldrich Chemical Co. and used as GC calibration standards without purification. *N,N'*-di(tert-butyl)ethylenediamine (**2e**) was purchased from Alfa Chemical Co. *N*-Isobutylethanolamine (**1b**) [6], *N*-sec-butylethanolamine (**1c**) [6], *N*-neopentylethanolamine (**1d**) [7], *N,N'*-di(iso-butyl)ethylenediamine (**2b**) [8], *N,N'*-di(sec-butyl)ethylenediamine (**2c**) [8], and *N,N'*-di(tert-butyl)piperazine (**3e**) [9] were synthesized according to literature procedures. The remaining GC standards were new compounds and were synthesized by using modified literature methods.

Catalytic reactions

Reactions were run in a 22 mL Parr bomb constructed of stainless steel and stirred by means of a magnetic stirring bar. The bomb was charged in a nitrogen filled glove box with $RuCl_2(PPh_3)_3$ (0.12 g, ca. 1.3×10^{-4} mol), ethylene glycol (5 mL), amine (usually ca. 1.2×10^{-2} mol) and *N*-methylpyrrolidinone (0.51 g) as internal standard. The bomb was sealed in the glove box and then placed in a previously heated oil bath (ca. 120 °C). After stirring at this temperature for 2–2.5 h, the bomb was cooled, vented, opened, and the contents analyzed by gas chromatography. Analyses were performed using a copper column (3.2 mm × 180 cm) packed with 15% Carbowax 20M on Gaschrom Q. In the case of methylamine, a solution of known concentration was prepared by bubbling the amine through ethylene glycol (containing internal standard) until the desired weight gain had been achieved. This solution was prepared in the absence of air and was then added to the bomb under N_2. When higher amine to glycol ratios were used, these were obtained by holding the volume of ethylene glycol constant and adding more amine.

Synthesis of amines

Since only enough material was needed to prepare GC standards, the following procedures were not optimized. NMR spectra were obtained using an IBM SY-200 FT spectrometer operating at 200 MHz.

N,N'-*di(sec-butyl)piperazine (**3c**).* A 50% $NaOH/H_2O$ solution (20 mL) was added to 10.8 g (0.125 mol) piperazine in 10 mL EtOH. An additional 10 mL of water was added in order to redissolve the NaOH that precipitated and two liquid phases formed. To this mixture was added 34.2 g (0.250 mol) 2-bromobutane and the mixture was refluxed for 4 h. At the end of this time, GC analysis showed unreacted piperazine, mono-alkylated product and the desired di-alkylated product. An additional 16 g (0.12 mol) of alkyl bromide was added and the mixture was heated for 24 h. The ethanol layer was collected and the aqueous layer was washed with toluene (3 × 20 mL). Distillation of the combined organic layers gave 2.5 g (14%) *N*-sec-butylpiperazine (b.p. 69–69.5 °C at 8 torr) and 8.0 g (32%) **3c** (b.p. 101–102 °C at 8 torr). Elemental analysis. Found: C, 72.44; H, 13.27; N, 14.18. $C_{12}H_{26}N_2$ calc.: C, 72.67; H, 13.21; N, 14.12%. ^1H NMR ($CDCl_3$): δ 0.79 (t, 6H); 0.88 (d, 6H); 1.17 (m, 2H); 1.49 (m, 2H); 2.29 (q of t, 2H); 2.43 (br s, 8H).

N,N'-*di(isobutyl)piperazine (**3b**).* This was synthesized similarly to **3c**; however, separation of **3b** from the mono-alkylated product proved difficult. A very small

amount of **3b** was obtained by distillation (b.p. 83-85 °C at 7 torr). ^{1}H NMR ($CDCl_3$: δ 0.85 (d, 12H); 1.72 (m, 2H); 2.03 (d, 4H); 2.37 (br s, 8H).

N,N′-*di(neopentyl)ethylenediamine (2d).* A stirred solution of 13.0 g neopentylamine (0.15 mol) and 2 mL water in 13 mL ethanol was treated with 13.5 g dibromoethane (0.07 mol) over the course of 5 min. The solution was refluxed for 1 h, cooled, and allowed to stand overnight. The resulting mixture (containing a white solid) was treated with 25 mL 50% NaOH. Extraction with toluene (3 × 20 mL) followed by vacuum distillation gave 5.1 g (36%) of the product distilling at 85 °C at 11 torr. Elemental analysis. Found: C, 71.40; H, 14.01; N, 13.66. $C_{12}H_{28}N_2$ calc.: C, 71.93; H, 14.08; N, 13.98%. ^{1}H NMR ($CDCl_3$): δ 0.90 (s, 18H); 1.18 (br, s, 2H); 2.35 (s, 4H); 2.72 (s, 4H).

N,N′-*di(neopentyl)piperazine (3d).* A solution of 13 mL methanol, 2 mL water, 13.0 g neopentylamine (0.15 mol) and 28.0 g dibromoethane (0.15 mol) was refluxed for 40 h. The solution was cooled to room temperature and GC analysis indicated that substantial amounts of starting material were present. Addition of 12 g of a 50% NaOH (aq) solution resulted in a two-phase system, which was refluxed overnight. On cooling, the mass solidified. Another 10 mL of 50% NaOH solution was added and enough Et_2O and water were added to loosen the mass sufficiently for transfer to a separatory funnel. Repeated extractions with Et_2O (~ 300 mL total) succeeded in dissolving all of the solid. The yellow-brown Et_2O solution was taken to dryness *in vacuo*. The brown solid was dissolved in THF/toluene (~ 1 : 1) and passed through a 1 cm × 15 cm bed of basic alumina. This lightened the color somewhat and the solution was again taken to dryness. White flakes were obtained by recrystallization from 1 : 1 MeOH/toluene. Yield: 2.2 g (13%). Elemental analysis. Found: C, 74.29; H, 13.17; N 12.31. $C_{14}H_{30}N_2$ calc.: C, 74.27; H, 13.36; N, 12.37%. ^{1}H NMR ($CDCl_3$): δ 0.86 (s, 18H); 2.00 (s, 4H); 2.47 (s, 8H).

Results and discussion

Catalysis by the Ru–PPh_3 system

The reaction of primary amines with ethylene glycol in the presence of $RuCl_2(PPh_3)_3$ proceeds smoothly to give aminoalcohols, diamines, and piperazines. At first glance, no clear selectivity pattern is evident. Unlike reactions of secondary amines with ethylene glycol, in which $RuCl_2(PPh_3)_3$ gives clean conversion to aminoalcohols, regardless of the amine, the selectivity of the reactions involving primary amines is strongly dependent on the alkyl group on the amine.

$$HOCH_2CH_2OH + RNH_2 \xrightarrow[\substack{120-130\,^\circ C\\ 2-2.5\ h}]{RuCl_2(PPh_3)_3} RNHCH_2CH_2OH + RNHCH_2CH_2NHR + \text{piperazine} \quad (1)$$

(1) **(2)** **(3)**

(**a**: R = methyl; **b**: R = iso-butyl; **c**: R = sec-butyl; **d**: R = neopentyl (Np); **e**: R = tert-butyl)

Table 1

Results of ethylene glycol (EG) reactions with primary amines [a]

R	EG : Amine	temp. (°C)	Selectivity (%)			conv. (%)	S_t [b] (%)	r'
			1	**2**	**3**			
Methyl	6.7:1	119	2	75	5	79	82	0.98
Methyl	5.9:1	130	4	44	33	96	81	0.95
iso-Butyl	7.7:1	123	12	24	35	100	72	0.82
ios-Butyl	2.0:1	125	12	73	4	90	89	0.86
sec-Butyl	7.7:1	123	48	21	16	99	85	0.44
sec-Butyl	2.0:1	120	51	33	4	46	93	0.40

[a] All reactions 2–2.5 h with 1 mol% catalyst. [b] S_t represents total selectivity to the three products shown and indicates the degree of amine accountability in the reactions.

We have previously defined [2] a selectivity ratio to characterize the selectivities seen for ethylene glycol amination:

$$r = \frac{\text{selectivity to di-amination}}{\text{sel. to di-amination} + \text{sel. to mono-amination}}$$

In the case of secondary amines, calculation of r is straightforward:

$$r = \frac{\text{selectivity to diamine}}{\text{sel. to diamine} + \text{sel. to aminoalcohol}}$$

In contrast, when primary amines are used, the formation of substituted piperazines introduces a complication not present with secondary amines, since, not surprisingly, the formation of piperazines is very sensitive to conversion. For example, data in Table 1 show that in the case of methylamine, at 79% conversion, 75% selectivity to **2a** and 5% to **3a** are obtained. If the conversion is increased to 96%, diamine selectivity falls to 44% while that of the piperazine increases to 33%. The selectivity to **1a** is relatively unchanged with conversion. This suggests that the diamine is being converted to the piperazine, and that di-amination can give either **2** or **3**, depending on the conversion.

If we assume that piperazine formation is simply a further consequence of di-amination, it is useful to define a new selectivity ratio. Because the diamines appear to be cleanly reacting at high conversions to form piperazines, the modified selectivity ratio can now be defined as:

$$r' = \frac{\text{selectivity to } \mathbf{2} + \text{selectivity to } \mathbf{3}}{\text{sel. to } \mathbf{1} + \text{sel. to } \mathbf{2} + \text{sel. to } \mathbf{3}}$$

When r' is calculated in this fashion, clear selectivity patterns emerge, even at significantly different conversions. The data shown in Table 1 reveal that the seemingly random selectivities for the formation of **1**, **2**, and **3** derivatives from the several primary amines are quite consistent for a given amine when measured by r'. Noting that an r' value of zero indicates complete mono-amination and an r' value of one designates complete di-amination, the selectivity to mono-amination increases in the order $MeNH_2$ < iso-$BuNH_2$ < sec-$BuNH_2$.

Inspection of this selectivity order suggests strong steric dependence, since it is the same order as that of increasing bulk of the alkyl group. This is more fully

Table 2

Effect of alkyl group on selectivities of reactions of ethylene glycol with primary amines [a]

R	Selectivity (%)			conv. (%)	S_t (%)	r'
	1	2	3			
Methyl	2	75	5	79	82	0.98
iso-Butyl	12	24	35	100	72	0.82
sec-Butyl	48	21	16	99	85	0.43
Neopentyl	46	21	5	100	72	0.36
tert-Butyl	94	0	0	88	94	0.00

[a] Conditions as in Table 1, ca. 120 °C, EG : Amine ca. 7–8.

shown in Table 2, where selectivity data for five amines is given. The data are arranged in order of increasing selectivity to mono-amination, as indicated by the value of r'. Again, the trend is clear. The bulkier the alkyl group, the higher the selectivity to mono-amination.

Selectivity and steric factors

This selectivity trend is quantified more fully in Table 3. The alkyl groups are once again listed in order of increasing size, along with the corresponding r' values. Also listed are the linear-free-energy parameters E_s and E_s^c. The values of E_s are taken from the work of Taft and represent the steric factors obtained from acid catalyzed ester hydrolysis reactions [10]. It is believed that the rates of these hydrolysis reactions are largely sterically controlled and decreasing values of E_s indicate increased steric hindrance. Comparison of E_s values in Table 3 with r' values shows a clear relationship, with neopentyl being the only anomaly.

The neopentyl group, however, falls into line if the so-called "corrected" E_s^c values of Hancock [11] are considered. The E_s^c factors take into account hyperconjucation effects in the ester hydrolysis reaction and separate these effects from the actual steric effects. An extensive tabulation of E_s^c values has been published by Fujita and co-workers [12].

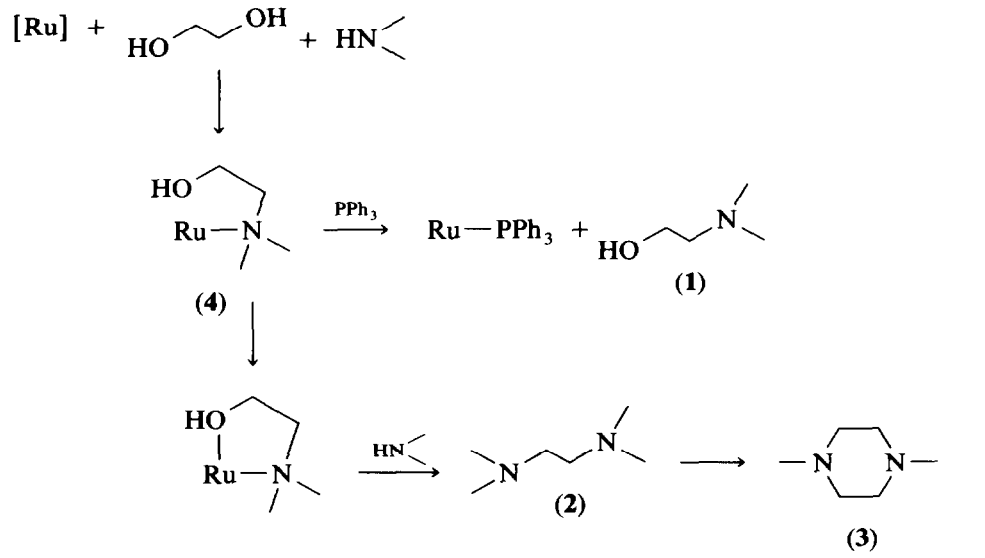
Not surprisingly, the steric parameters of primary amines closely parallel the nucleophilicity of these amines. The nucleophilicity of many amines has been determined and tabulated by Hall [13]. These values are also listed in Table 3, and

Table 3

Comparison of selectivity ratio (r') of reactions of primary amines with ethylene glycol and steric and nucleophilic parameters

R	r'	(E_s) [a]	(E_s^c) [b]	n [c]
Methyl	0.98	0.00	0.00	5.21
iso-Butyl	0.82	−0.93	−1.24	4.99
sec-Butyl	0.43	−1.13	−1.74	4.66
Neopentyl	0.36	−1.74	−2.05	–
tert-Butyl	0.00	−1.54	−2.46	4.14

[a] Taft's steric substituent constant (Ref. 10). [b] Hancock's "corrected" steric constant (Ref. 12). [c] Hall's nucleophilic constant for H_2NR (Ref. 13).



Scheme 1

they too are seen to reflect the selectivities seen in glycol amination reactions. As the nucleophilicity parameter falls, so too does selectivity to di-amination.

This is consistent with the reaction scheme presented earlier for secondary amines [2b]. The selectivity between mono- and di-amination appears to be controlled by the stability of the intermediate alkanolamine complex **4**. In the case of secondary amines, which give tertiary alkanolamines as products when PPh_3 is present, the stability of this complex is relatively poor and the free **1** can be liberated because of further destabilization by the phosphine. Primary amines, however, would give secondary alkanolamines, which are less sterically hindered and thus, better ligands. Because of this, they are not as easily dissociated and reside in the coordination sphere of the ruthenium long enough to undergo a second amination. The alkanolamine complex stability is, of course, dependent on the size of the alkyl group on the amine. Thus, bulky alkyl groups lead to dissociation of **1** while small alkyl groups give a more stable complex (**4**) and di-amination results. Additionally, the higher nucleophilicity of the smaller amines should make all the amination steps more favorable and this may be more critical in the second amination step.

While the data we collected were not intended for rigorous kinetic or physical organic chemical treatment, it is nevertheless interesting to construct a simple plot relating selectivity to steric parameter. For this purpose, we will define a new ratio:

$$r^* = \frac{\text{selectivity to } \mathbf{2} + \text{selectivity to } \mathbf{3}}{\text{selectivity to } \mathbf{1}}$$

This ratio is more suited to this type of treatment, since, if our conclusion that **2** and **3** can be grouped together as di-amination products is correct, r^* should be a measure of the relative rates of the di- and mono-amination reactions. (Our previous

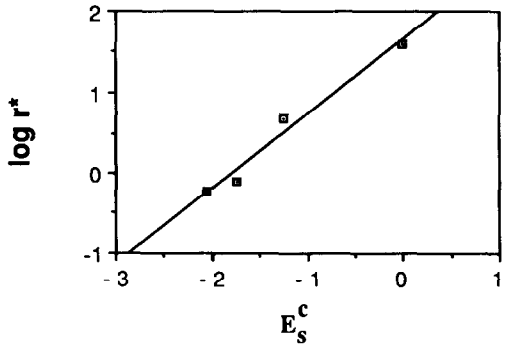


Fig. 1. Relationship between r^* and E_s^c for reactions of primary amines with ethylene glycol.

definitions of r and r' are merely convenient and practical measures of selectivity and have no specific kinetic meaning). When log r^* is plotted vs. E_s^c, a reasonably good correlation is obtained (Fig. 1) *. The slope (0.9, correlation coefficient = 0.97) is quite close to 1.0, demonstrating again the strong steric influences in these reactions.

Effect of added triphenylphosphine

We have previously shown that, at 120 °C, the presence of PPh_3 (PPh_3 : Ru > 1) greatly enhances the selectivity to **1** with secondary amines [2]. This effect is partially lost at higher temperatures; however, it can be regained by the addition of larger amounts of PPh_3 (PPh_3 : Ru ≥ 5) [2b,d]. Some selectivity enhancement can also be achieved with primary amines by the addition of phosphine. The effect of PPh_3 : Ru ratio for the reaction of sec-butylamine with ethylene glycol is shown in Table 4. This amine is not particularly selective for mono-amination with $RuCl_2(PPh_3)_3$ alone; however, high selectivity to mono-amination is achievable if a sufficiently high PPh_3 : Ru ratio is used. Unfortunately, the added phosphine also decreases catalyst activity at this temperature.

Triruthenium dodecacarbonyl as catalyst precursor

Jenner and co-workers have reported that $Ru_3(CO)_{12}$ in combination with PBu_3 at high temperatures catalyzes reactions of ethylene glycol with amines [5]. We too reported $Ru_3(CO)_{12}$ as an effective catalyst precursor for glycol aminations, and in

Table 4

Effect of excess triphenylphosphine on the reaction of sec-butyl amine with ethylene glycol

PPh_3 : Ru	Selectivity (%)			conv. (%)	r'
	1	**2**	**3**		
3.0	48	21	16	99	0.44
4.4	53	11	9	99	0.27
10.4	31	5	–	19	0.14

* Data for R = tert-Butyl omitted, since $r^* = 0$.

Table 5

$Ru_3(CO)_{12}$ as catalyst precursor [a]

R	EG : Amine	Selectivity (%)			conv. (%)	S_t (%)	
		1	2	3			
Methyl	2.0 : 1	10	9	31	57	50	0.80
Methyl	2.9 : 1	3	2	20	78	25	0.88
Methyl	2.0 : 1	12	0	45	73	57	0.79
Methyl	2.3 : 1	12	5	40	68	57	0.79
iso-Butyl	3.2 : 1	43	21	20	75	84	0.49
iso-Butyl	3.0 : 1	26	7	27	69	60	0.57
iso-Butyl	3.1 : 1	43	20	19	76	82	0.48
sec-Butyl	2.7 : 1	34	7	28	91	69	0.51
sec-Butyl	3.1 : 1	27	33	26	68	86	0.67
tert-Butyl	2.9 : 1	12	84	3	34	99	0.88
tert-Butyl	3.0 : 1	42	37	14	100	93	0.55

[a] Conditons: 200 °C, 2h, 500 psi H_2.

our case, we observed activity without added phospine ligand [14]. The results of reactions of primary amine with ethylene glycol at 200 °C in the presence of $Ru_3(CO)_{12}$ are shown in Table 5. Note that no clear ordering of selectivity is seen at these temperatures and with this catalyst. It should also be noted that, unlike the Ru^{II} systems, the $Ru_3(CO)_{12}$ catalyst system is not active at lower temperatures This emphasizes the importance of having a catalyst which is active enough that lower temperatures can be used to enhance selectivity control. In addition, catalyst activity appears to vary from run to run with the carbonyl system. This may be due to catalyst decomposition, and, as reported by Jenner, it may be desirable to add phosphine in order to stabilize the system.

Conclusion

The catalytic system obtained from $RuCl_2(PPh_3)_3$, ethylene glycol, and amines is extraordinarily active at relatively low temperatures. This activity at low temperatures allows highly selective reactions to occur—reactions in which the selectivity is very finely balanced and which can be easily altered. The effect of steric factors is extremely important in this catalytic chemistry and indications are that the selectivity can be predicted by using steric parameters available in the literature.

Acknowledgements

I'd like to thank George Zalepa and LeRoy Whinnery for able technical assistance, Ann Kotz for obtaining NMR spectra, and Air Products and Chemicals, Inc. for permission to publish this work. I'd also like to thank Guido Pez and Kevin Lassila for helpful discussions.

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