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$(Ph_3P)_3RuCl_2$ Catalyzed Equilibration and Elimination of α-Chloro-N-Tosyl-2-Pyrrolidinones: A Unique Route to Unsaturated 2-Pyrrolidinones.

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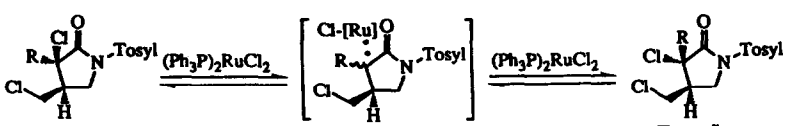
Abstract: Equilibration studies showed that chlorinated N-tosyl amides cyclized under primarily kinetic control. Modification of the ruthenium complex catalyzed the formation of unsaturated 2-pyrrolidinones.

In an earlier communication, we reported that a variety of α-chloro N-tosyl amides underwent $(Ph_3P)_3RuCl_2$ catalyzed cyclizations. The dominant diastereoselectivity in these reactions positioned the largest substituent at C(2) trans to the chloromethyl on the 2-pyrrolidinone ring. Weinreb[1] noted ruthenium catalyzed isomerizations in his study of exocyclic α–chloro esters. He postulated that α–chlorine abstraction accounted for equilibration. Itoh and Nagashima[2] later demonstrated that α,α-dichloro-2-pyrrolidinones were reactive with ruthenium (II) complexes showing that additional carbon-carbon bonds can be constructed adjacent to the carbonyl. These considerations prompted us to characterize the thermodydnamic behavior of diastereomeric N-tosyl 2-pyrrolidinones in the presence of ruthenium catalyst. We report that equilibration occurs, but that the rate of equilibration is very slow with respect to cyclization. We also find that at high ruthenium catalyst concentrations equilibration is partially inhibited and the formation of unsaturated 2-pyrrolidinones is promoted.

Two methods were used to study the equilibration. The first method gave the rates of equilibration and the final equilibrium constant. Dissolution of either the cis or trans isomer of N-tosyl 2-pyrrolidinone **1-4** (0.12 M) under anaerobic conditions in a stock solution of $(Ph_3P)_3RuCl_2$ (2.4×10^{-3}M in C_6D_6) resulted in homogeneous solutions of catalyst and substrate. Heating these mixtures to either 135 °C, for **1**, or 100 °C for **2-4** effected equilibration. The progress of equilibration was measured by ^1H NMR integration against an internal standard of benzene (eq 1). The concentration of ruthenium catalyst in this study was approximately one-third that used for normal cyclization catalysis because at this concentration no insoluble dimeric ruthenium (II) complex $[(Ph_3P)_2\,RuCl_2]_2$ formed.[3] Lower concentration of catalyst provided complete equilibration (vide infra).



Cis Isomer — Trans Isomer (1)

1 R = H **2** R = CH_3
3 R = iPr ($(CH_3)_2CH$) **4** R = t-Amyl ($CH_3CH_2(CH_3)_2C$)

Table 1 summarizes the forward and reverse rate constants for the equilibrations, the half-lives to equilibrium, and the equilibrium cis : trans ratios. The experimental data were fit to the kinetic model shown in equation 1 using GEAR,[4] and k_1 and k_{-1} were determined. The concentrations of **1-3** were easily measured,

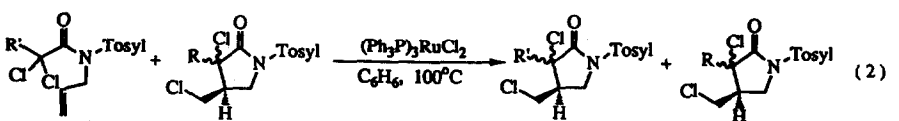
Table 1. Equilibration Data for Alkyl N-Tosyl 2-Pyrrolidinones.

Entry	N-Tosyl Pyrrolidinone	Starting Diastereomeric Isomer	Equilibration Temperature °C ± 0.2 °	k_1 rate constant, k_{-1} rate constant ($x10^3$ $M^{-1}s^{-1}$)	Half-Life to Equilibrium (h)	Final Cis : Trans Ratio[a] (Cyclization Ratio)[b]
1	1	Cis	135	8.4 ± 0.4 3.6 ± 0.2	6.7	32 : 68 (21 : 79)
2		Trans	135	3.1 ± 0.2 7.3 ± 0.4	7.7	33 : 67
3	2	Cis	100	24.8 ± 1.2 6.5 ± 0.3	2.6	20 : 80 (27 : 73)
4		Trans	100	6.5 ± 0.5 24.4 ± 1.9	2.6	19 : 81
5	3	Cis	100	1.1 ± 0.09 10.5 ± 0.8	6.9	91 : 9 (77 : 23)
6		Trans	100	9.5 ± 0.5 0.84 ± 0.04	7.8	90 : 10
7	4	Cis	100	----	----	>100 : 1[c] (>100 : 1)

[a] Measured against internal standard of benzene. [b] See preceding article. [c] Solutions heated in excess of 2 weeks at 100 °C

while pyrrolidinone **4** showed no new diastereomer. Further studies suggested that **4** equilibrated but with very high cis selectivity.

The second equilibration method required adding purified α-chloro-2-pyrrolidinone to mixtures of N-tosyl amide and ruthenium catalyst. These mixtures were heated allowing the pyrrolidinone and amide substrates to compete for the catalyst (eq 2). Three mixtures were studied, each utilizing the minor diastereomer at equilibrium. **Cis 1** (0.026 M) was added to a solution containing N-tosyl amide **5** (0.09 M) and catalyst (0.0024 M), and the mixture was heated to 100 °C. After 4 h, 65% of the amide was converted to the corresponding 2-pyrrolidinone and 3% of **cis 1** isomerized to **trans 1**. Under similar conditions, **cis 2** was added to **6** and catalyst , and **trans 3** was added to **5** and catalyst. Both mixtures showed >60% conversion to the pyrrolidinone after heating. These mixtures also showed that **cis 2** isomerized 54% to the trans isomer, while **trans 3** isomerized 4% to the cis isomer.



5 R' = CH_3
6 R' = iPr

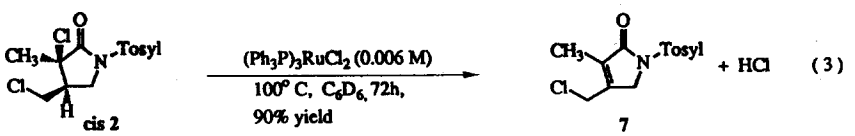
(2)

Two significant conclusions can be drawn from these equilibration studies. First, within the time frame of a normal cyclization catalysis, 4 h at 100 °C, α-chloro 2-pyrrolidinones equilibrate at least to a small extent. It is clear that cyclization diastereoselection is somewhat less than kinetic selectivity because of subsequent partial equilibration. Using the rate constants for equilibration a corrected kinetic selectivity of 16: 84 for **cis 1: trans 1** followed by isomerization would give the observed 21 : 79 selectivity. Similarly, kinetic selectivity of 42: 58 for **2** and 71: 29 for **3** followed by isomerization give the observed selectivity of 27: 73 for **2** and 77: 23 for **3**. Experimental data support these calculations since pyrrolidinones **1** and **3** equilibrate <5% while **2** equilibrates

extensively. This indicates that the ruthenium (II) catalyzed cyclization of N-tosyl amides is primarily under kinetic control. However, caution must be used in assigning the origin of stereochemistry.

Secondly, these studies show that Weinreb's speculation about α-chlorine abstraction is the most reasonable mechanism for equilibration. The methyl substituted 2-pyrrolidinone equilibrates about 2.5 times faster than the hydrogen or isopropyl derivatives. This small but significant rate difference is inconsistent with a ring opening-ring closing mechanism since the rate-determining step in this mechanism must be abstraction of the chlorine atom from the primary carbon. Chlorine atom abstraction should be independent of the substituent at C(2). Alternatively, the rate of α–chlorine abstraction depends upon the size of the substituent at C(2) and the stability of the incipient radical intermediate. Both effects are noted in these equilibration data. The isopropyl group in **3** impedes approach of the catalyst to C(2), slowing the rate of abstraction, while in **1** the hydrogen at C(2) is less effective at stabilizing the radical intermediate than an alkyl substituent. As a result, the rate of equilibration is reduced.

During this study a surprising catalyst concentration effect was noted. As the concentration of $(Ph_3P)_3RuCl_2$ increased the extent of isomerization decreased. For example, when a solution of **cis 2** (0.12 M) and catalyst (0.006 M) was heated to 100 °C the starting 2-pyrrolidinone rapidly equilibrated to a 54 : 46 mixture of cis and trans isomers over 4 h. Over the next 14 h no change in the mixture occurred. Additional heating resulted in a red-orange solution containing a 20 : 80 mixture of isomers and a 75% yield of a new product identified as the unsaturated 2-pyrrolidinone **7** (eq 3). A 90% yield of **7** was isolated after 72 h of heating. The ^1H NMR spectrum of **7** showed two broad singlets (δ 3.96 and 3.22) for the two sets of methylene protons. Purified **7** showed a carbonyl stretch of 1727 cm^{-1} consistent with a conjugated carbonyl system.[5]

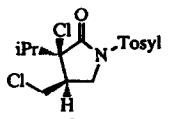
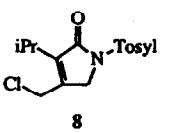
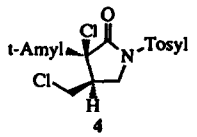
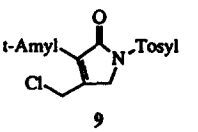


(3)

The most reasonable explanation for this concentration effect is that two or more ruthenium complexes interact forming new complex(es) which are inactive towards equilibration but may catalyze the elimination of HCl. The $(Ph_3P)_3RuCl_2$ concentration effect was duplicated in a two-step process. Equilibration of **cis 2** with 0.0024 M catalyst yielded a 20 : 80 mixture of isomers after 72 h and a 2% yield of **7**. Increasing the catalyst concentration to 0.006 M under inert conditions gave a solution which, over the next 72 h, gave a 62% of **7**. This concentration effect was exploited by conducting elimination reactions with **cis 3**, and **cis 4** (See Table 2.). Loss of HCl occurred at a competitive rate with equilibration in pyrrolidinone **3**, while **4** eliminated very slowly. The reactivity of **4** was particularly important since the quaternary carbon adjacent to C(2) opened the possibility of methyl migration to a carbocation intermediate.[6] Under no conditions were rearranged products found. Therefore, an open carbocation with a sufficient life time does not appear to be an important intermediate in this elimination.

Discussion: These results have two important implications for atom transfer catalysis. Equilibration studies on α-chloro-2-pyrrolidinones show that isomerization occurs by an α-chlorine atom abstraction and return mechanism. The rate of equilibration is highly dependent upon the substituent at C(2). A methyl group at C(2)

Table 2. Elimination Results From Alkyl Substituted 2-Pyrrolidinones Using 0.006 M Catalyst.

Substrate	Reaction Time (h)	Product	% Yield
 3	20	 8	92
 4	360	 9	88

appears to be the optimal match of size and radical stabilizing effects. As a consequence, N-tosyl amide **5** cyclizes under thermodynamic control. α-Chloro-N-tosyl amides containing either hydrogen or larger alkyl groups at C(2) appear to cyclize under predominant kinetic control. This opens the possibility of using diastereoselectivity as a tool to study the mechanistic details of ruthenium catalyzed cyclizations. Secondly, ruthenium-ruthenium interactions are fundamentally important for understanding this catalysis. A threshold concentration of catalyst, as low as 0.006 M, can produce species which are inactive toward isomerization. Cotton recently characterized chloro-bridged ruthenium dimers with mixed III and II oxidation states.[7] These complexes have interesting physical and redox properties. We plan to investigate the catalytic properties of these dimeric complexes in both the cyclization and elimination catalysis reactions and we hope to report these results in the future.

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5. Spectral data for **4**: ^{1}H NMR (C_6D_6, 200 MHz): 1.15 (s, 3H, *CH*$_3$), 1.77 (s, 3H, Ph-*CH*$_3$), 3.22 (s, 2H, *CH*$_2$-N), 3.97 (s, 2H, *CH*$_2$-Cl), 6.72 (d, J= 8.4 Hz), 8.10 (d, J= 8.4 Hz); IR (CH_2Cl_2): 1727(s); HRMS calc for $C_{13}H_{14}ClNO_3S$ 300.0461, found 300.0464. Data for **5**: ^{1}H NMR (C_6D_6, 200 MHz): 0.92 (d, J= 7.0 Hz, 6H, (*CH*$_3$)$_2$CH), 1.74 (s, 3H, Ph-*CH*$_3$), 2.32 (m, J= 7.0 Hz, 1H, (CH$_3$)$_2$*CH*), 3.36 (s, 2H, *CH*$_2$-N), 4.00 (s, 2H, *CH*$_2$-Cl), 6.67 (d, J= 8.3 Hz), 8.07 (d, J= 8.3 Hz); IR (CH_2Cl_2): 1724(s); HRMS calc for $C_{15}H_{18}ClNO_3S$ 327.0696, found 327.0721. Data for **6**: ^{1}H NMR (C_6D_6, 200 MHz): 0.50 (t, J= 7.5 Hz, 3H, (*CH*$_3$-CH$_2$), 1.04 (s, 6H, (*CH*$_3$)$_2$, 1.63 (q, J= 7.5 Hz, CH$_3$-*CH*$_2$), 1.75 (s, 3H, Ph-*CH*$_3$), 3.60 (s, 2H, *CH*$_2$-N), 4.02 (s, 2H, *CH*$_2$-Cl), 6.68 (d, J= 8.1 Hz), 8.06 (d, J= 8.1 Hz); IR (CH_2Cl_2): 1723(s); HRMS calc for $C_{17}H_{22}ClNO_3S$ 355.1009, found 355.1007.

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