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Intramolecular hydride transfer

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INTRAMOLECULAR HYDRIDE TRANSFER

A Thesis

Presented to

The Faculty of the Department of Chemistry

San Jose State University

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

By

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ABSTRACT

INTRAMOLECULAR HYDRIDE TRANSFER

by Vidya Baliga

Intramolecular hydride transfers over distances upto three carbon atoms are well documented. There are only a few examples of long (over 3 carbon atoms) range hydride transfer available in the literature. In this work, we have investigated the mechanism of the hydrolysis of 3-(2-furyl)acrylonitrile to γ -ketopimelic acid and compared it with similar hydrolyses of the nitro and carboxylic acid analogs. We have used deuterium labelling, a non-kinetic method, to investigate these reactions. A comparison with intermolecular reactions using an external source of hydride illustrates the efficiency of the intramolecular reaction.

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Introduction

Intramolecular 1,2 hydride transfer is a very common organic reaction with many literature precedents.^{1,2} 1,3-hydride transfers are also well documented.^{1,2} Intramolecular 1,*n*(*n*>3)-hydride transfer is a common reaction in medium rings and certain polycyclic systems.³ It has been argued³ that there is an optimum distance between transfer source and terminus in such compounds but in this thesis evidence will be aimed at proving that it is not only the distance but also the angle or the trajectory of the hydride shift with respect to the electrophile which determines whether the reaction is favored. In acyclic systems, 1,*n*(*n*>3)-hydride shifts are less common³ but the functionality present in the chain may encourage population of those conformations necessary for such shifts to occur. Scheme I³ shows a reasonable mechanism for an acid catalyzed rearrangement of the α,β -unsaturated ketone **1**. The mechanism undoubtedly involves an intramolecular 1,5-hydride shift, assisted by coordination of the boron trifluoride to the carbonyl oxygen and the stability of the resulting anisylc carbocation. A deuterium labelling experiment was consistent with this proposed mechanism.

Another literature example of a long range hydride shift is the Huang-Minlon reduction⁴ of 7- α -hydroxymethylbicyclo[3.3.1]-nonane-3-one (**2**) which gave 7- β -methyl bicyclo[3.3.1]-nonan-3- β -ol (**3**), the major product formed as a result of the transannular 1,6-hydride shift. The intramolecular hydride shift is triggered by relief of the steric strain in the system followed by inversion of the configuration α to the carbonyl (Scheme II). The reduction of the corresponding acetate under the same condition also gave the same

Scheme I

result. A base catalyzed intramolecular 1,6 hydride shift followed by epimerization α to the ketone (Scheme II) was postulated to explain the formation of the major product. This characteristic intramolecular hydride shifts was triggered by relief of the steric strain in the system.

Scheme II

More evidence for stereoelectronic control is provided in the acid-catalyzed redox reactions of spiroketals.⁵ Tricyclic spiroketal **4** yields equatorial bicyclic ether aldehyde **5** specifically. Similarly **6**, **7**, and **8** give equatorial bicyclic ketone **9**. The acid catalyzed redox reactions can be explained by the opening of the spiroketals giving an hydroxy bicyclic oxenium ion intermediate to yield the bicyclic ether **5** or **9**. The stereospecific formation of the equatorial bicyclic ethers **5** and **9** can be explained if stereoelectronic effects are taken into consideration. Hydride transfer was assumed to take place with minimum energy only when an axial electron pair on oxygen in the final product was anti periplanar to the newly formed C-H bond(axial) (Scheme III).

Baldwin^{6,7} has pointed out the importance of trajectory considerations in synthetic organic chemistry. He devised a set of qualitative rules which are accepted as useful guidelines to predict the relative facility of ring-forming reactions. He describes a ring-forming process with the prefix *exo* when the breaking bond is exocyclic to the ring which is formed, and *endo* when the breaking bond is endocyclic to the ring which is formed (Scheme IV). Furthermore, a numerical prefix is used to describe the ring size of the cyclic transition state and finally, the suffixes *tet*, *trig*, and *dig* to indicate the geometry of the electrophilic carbon atom undergoing the ring closure reaction. These suffixes refer to tetrahedral, trigonal and digonal carbon atoms respectively. The physical basis of the rules lies in the stereoelectronic requirements of the transition states for the various tetrahedral, trigonal and digonal ring closure processes. Since the linking chain restricts the relative motion of the terminal.

Scheme III

Scheme IV

Exo -Tet

Endo- Tet

Exo-Trig

Endo-Trig

Exo -Dig

Endo- Dig

groups X and Y, the nature of the chain and hence the ring size will determine whether X and Y can attain the transition state geometry required for ring closure. Favored ring closures are those in which the length and nature of the linking chain enables the terminal atoms to achieve the required trajectories to form the final ring bond. Disfavored cases require severe distortion of bond angles and distances to achieve such trajectories; consequently alternative reaction pathways, if available, will dominate and the desired ring closure will be difficult, if not impossible.

Baldwin's rules state: (a) 3 to 7-*exo-tet* are all favored processes and 5 to 6-*endo-tet* are disfavored; (b) 3 to 7-*exo-trig* are all favored processes and 3 to 5-*endo-trig* are disfavored but 6 to 7-*endo-trig* are favored; (c) 3 to 4-*exo-dig* are disfavored processes but 5 to 7-*exo-dig* are favored and 3 to 7-*endo-dig* are favored. These rules are most applicable to second row nucleophiles. **Intramolecular hydride shifts are not specifically covered by existing rules.**

The reaction which drew our attention was the abnormal hydrolysis of 2-(2-nitrovinyl) furan (**10**) to 4-oxo-6-nitro hexanoic acid first reported in 1909 by Thiele and Landers⁸ (eq 1).

We consider this reaction as abnormal hydrolysis because the anticipated product was 4-oxo-6-nitro-5-hexenal. Instead C_a of the furan ring is oxidized and C_e and C_f are reduced in the final product. There is no net change in the overall oxidation state during the reaction. A redox reaction, assumed to be intramolecular in nature has taken place. A detailed investigation of the mechanism of the reaction (eq 1) was performed by Bansal.⁹

This thesis presents a mechanistic study of the acid catalyzed hydrolysis of 3-(2-furyl)acrylonitrile (**11**) to the product γ -keto pimelic acid (**12**) and 3-(2-furyl)acrylic acid to the same product. A ketoaldehyde is the presumed

intermediate in this transformation (eq 2).

There has been a net hydride shift during the hydrolysis from C_a to either C_e or C_f. Assuming that hydride shift is indeed an intramolecular process we examined the three distinct mechanistic possibilities for the conversion of the presumed intermediate to the final product (Scheme V): (a) a 1,6-shift (a 7-*endo-trig* reaction), (b) a 1,5-shift (a 6-*exo-trig* reaction), or (c) a 1,4-shift (a 5-*exo-trig* reaction) followed by a 1,2-shift.

Our short term goal was to determine which of the three mechanisms **a**, **b** or **c** is operating under the reactions conditions. We decided to investigate this by deuterium labelling studies.

Another goal was to find the intrinsic *electronic* preference of any α,β -unsaturated hydride acceptor by use of the truncated substrate (lacking the internal aldehyde) and an external source of hydride such as formaldehyde or formic acid.

Our long-term goal is to synthesize additional model compounds to study the roles played by stereoelectronic factors in this reaction. The importance, if any, of stereoelectronic factors, which are known to be important in 1,2-hydride shifts, has not been systematically assessed in hydride transfers over distances greater than two carbon atoms.

Scheme V

Results and Discussion

To determine the pathway of hydride transfer in the hydrolysis of **11** we could have labelled C_a with deuterium. Bansal⁹ performed a similar study for nitrovinylfuran by starting with an unlabelled starting material and performing the reaction in a labelled reaction medium (DCl/ D_2O).

Therefore, we used the same approach to get the mechanistic information in the hydrolyses of substituted alkenyl furans.

It was essential to examine the product **12** for the presence of any exchangeable protons under the hydrolysis reaction conditions. The control experiment showed exchange (via enolization) only α to the ketone (eq 3).

In the DCl hydrolysis of the unlabelled substrate, the NMR spectrum of the product clearly showed that it had retained only two hydrogens α hydrogen next to each carboxylic acid (eq 4)

The results expected for each of the three possible mechanisms are shown in Scheme VI. The NMR spectrum of the product clearly showed that

the product had retained only two hydrogens -- one on C_b and the other on C_f, indicating that the shift was occurring either via pathway **b** or **c** (Scheme VI).

Scheme VI

The acid catalyzed hydrolysis of furyl acrylic acid (**13**) was also carried out under the same reaction conditions and the same product γ -keto pimelic acid **12** was obtained (eq 5).

An analogous reaction was reported by Singleton¹⁰ in 1948. He carried out synthesis of diethyl- γ -keto pimelate from furyl acrylic acid in hydrochloric acid/ethanol. The result of our study of hydrolysis of substituted alkenyl

furans was consistent with the results of Bansal⁹ who performed a similar reaction using nitrovinyl furan as the starting material.

In order to get baseline data on intermolecular hydride transfer we studied the reactions of α,β -unsaturated hydride acceptors and an external source of hydride in an acidic medium. We used formaldehyde and formic acid as hydride donors. The α,β -unsaturated substrates used in our study included crotonic acid, crotonitrile, cinnamic acid, cinnamitrile and β -nitrostyrene. We wanted to explore the intrinsic electronic preference of the hydride in these α,β -unsaturated compounds. It was clear that there should be no doubt about the importance of the stereoelectronic effect should the intramolecular hydride shift exhibit a site preference which differed from the intermolecular analog.

The results obtained from these intermolecular reactions are shown in Table I. To keep the reaction conditions of the intermolecular reactions as close as possible to that used in the intramolecular reactions, hydrochloric acid was chosen as the acid catalyst and formaldehyde as the external source of hydride. The product did not undergo reduction of the double bond as expected, but instead there was a conjugate addition of chloride. In an attempt to get the reduced product, the concentration of the formaldehyde was increased tenfold but the desired reaction, namely reduction of the double bond, was not achieved. The reaction was then carried out with formic acid (HCOOH) as the hydride donor. Initially, we used one equivalent of formic acid but since that did not give the desired reduced product, the concentration of the formic acid was then increased tenfold. The product obtained was still a conjugate addition of the hydrochloric acid (HCl) or no reaction in substrates like *trans* cinnamic acid. The same reaction was tried

with sulphuric acid as the acid catalyst instead of hydrochloric with the rationale that since bisulphate (HSO_4^-) is not as good a nucleophile as chloride (Cl^-) the corresponding reduced product might be obtained. However, none of these reactions gave the expected product. This can be rationalized on the basis that the rates of intramolecular and the corresponding intermolecular reaction vary so greatly. In intramolecular reactions, if the migrating hydride can acquire the required trajectory to form the final ring bond the reaction goes to completion in a relatively short time. On the other hand in the intermolecular reactions using an external hydride source the reaction has to proceed via a highly organized transition state. The considerable loss of entropy necessary to reach the transition state is the probable explanation for not obtaining the reduced product in intermolecular reaction. The literature¹¹ shows that the intramolecular reactions in certain cases are 10^8 times faster than the corresponding intermolecular reactions. The known reactions in which formic acid (HCOOH) and formaldehyde (H_2CO) are used as hydride donors are the Leuckart's Reaction¹² and the Escweiler-Clark Reaction.¹²

Table I. Attempts at intermolecular hydride transfer.

SUBSTRATES	REAGENTS	PRODUCT(S)
Crotonic Acid	HCl, H ₂ CO (1.1 eq.)	3-Chlorobutyric acid
Crotononitrile	HCl, H ₂ CO (1.1 eq.)	Crotonic acid and 3-chlorobutyric acid
Cinnamic Acid	HCl, H ₂ CO (1.1 eq.)	Recovered starting material
Cinnamionitrile	HCl, H ₂ CO (1.1 eq.)	<i>Cis</i> and <i>trans</i> cinnamic acid
β-nitrostyrene	HCl, H ₂ CO (1.1 eq.)	Recovered starting material

a). The reactions were done at 50-60 °C. b). The reactions were also performed using the following variations: (i) HCl, HCOOH (10 equivalent) (ii) H₂SO₄, H₂CO (1.1 equivalent) (iii) H₂SO₄, H₂CO (10 equivalent) (iv) H₂SO₄, HCOOH (1 equivalent) (v) H₂SO₄, HCOOH (10 equivalent). In none of these cases did we find any evidence of reduction of the double bond.

Conclusion

Our experiments have ruled out 1,6 hydride shift in the hydrolyses of 3-(2-furyl)acrylonitrile and 3-(2-furyl)acrylic acid. By means of deuterium labelling we have shown that in the hydrolysis of 3-(2-furyl) acrylonitrile **11** the hydride migrates from C_a to C_e. Thus pathway a in Scheme V, one of the plausible mechanisms for the hydride shift, has been eliminated. Our experiments have shown that the hydride migrates to C_e whether the electron withdrawing substituent in 2-alkenyl furan is nitro⁹ or carboxylic acid. The nitro group is a better electron withdrawing group than the ketone, whereas the carboxylic acid is a poorer electron withdrawing group than the ketone. The hydride migrates to C_e irrespective of the electron withdrawing group attached to the double bond in substituted alkenyl furans. Thus it is reasonable to conclude that it is not the electron withdrawing group which is affecting the hydride migration in the acid catalyzed hydrolysis of 2-alkenyl furans.

Our study shows that in intramolecular reactions of substituted vinyl furans the reaction is completed within one hour. The corresponding intermolecular reactions using a series of simple alkenes with different electron withdrawing groups and an external hydride source like formaldehyde and formic acid did not give the expected reduced products. By doing the intermolecular reactions with an external hydride source, under conditions similar to those used in our original hydrolysis of the nitrile **11**, we obtained either conjugate addition of chloride or we recovered the starting material.

Our work illustrates the efficiency of the intramolecular hydride in

reacting with the electrophilic site in an unsaturated conjugate system. Knowledge of stereoelectronic requirements of intramolecular hydride transfer may help us to understand biological reaction mechanisms. Enzymes are believed to act as exceedingly efficient catalysts by bringing together at the "active site" various basic, acidic or nucleophilic groups in the proper stereoelectronic alignment.

Additional work will involve distinguishing between mechanisms **b** and **c**. Model compounds which will allow us to choose between these two alternatives are shown in Scheme VII. If the unsaturated alcohol does not isomerize to the saturated ketone under the reaction conditions utilized for the original hydrolysis, then path **c** may be excluded. Similarly if the aldehyde lacking the keto group does not yield the saturated carboxylic acid then path **b** may be excluded (Scheme VII).

Further work on this project should investigate the endocyclic versus exocyclic selectivity, the ring size of the transition state and the relative abilities of different functional groups to activate conjugated alkenes as hydride acceptors. The structures which will eventually define the parameters governing intramolecular hydride transfer are systems in which two or more electrophilic sites compete for the migrating hydride (Fig. 1). Compounds must be synthesized in which differing electron withdrawing groups are placed at either end of the double bond as well as parallel structures in which the carbon chain length remains constant but the terminal and internal functional groups have had their sites of attachment exchanged. Examination of such pairs of compounds will yield unambiguous information about the character of intramolecular hydride shifts and the relative contributions of electronic and stereoelectronic control. The presumed intermediate aldehyde in the hydrolysis of acrylonitrile furan is an

Scheme VII

example of a difunctionalized alkene serving as an intramolecular hydride acceptor. Accordingly, both the functionally inverted alkene and the intermolecular analog need to be prepared in order to make a comparison.

Hydrolysis Intermediate
X= Electron Withdrawing Group

Inverted Functionality

Intermolecular Analog

Figure 1. Substrates for intramolecular hydride transfer

Experimental Section

General Procedures. Melting points were determined with a digital melting point apparatus Electrothermal AI 900 and are uncorrected. IR spectra were recorded on a Perkin-Elmer 710B Infrared Spectrophotometer. Band Positions are reported in reciprocal centimeters (cm^{-1}). ^1H NMR spectra were recorded in parts per million (δ) relative to TMS, on a 300 MHz QE Plus Spectrometer.

3-(2-Furyl)acrylonitrile (11)¹³. A mixture of freshly distilled furfural (22.12 g, 0.22 mol), 98% cyanoacetic acid (17.4 g, 0.20 mol), ammonium acetate (0.6 g), toluene (40 mL), and pyridine (22 mL) was placed in a 250-mL round-bottomed flask equipped with a Stark and Dean water trap and reflux condenser. The mixture was refluxed and the theoretical quantity of water was collected in the trap within approx. 1 h. Upon completion of the reflux period, the solvent was removed under reduced pressure (~ 16 mm) at a temperature of 160-200 $^{\circ}\text{C}$ (oil bath). The residue was distilled through a 19/22 reflux condenser packed with steel sponge and insulated with glass-wool and aluminium foil to give 16.9 g (71%) of a colorless liquid as a mixture of E:Z isomers ($\sim 1 : 2$); bp 123-124 $^{\circ}\text{C}/\sim 16$ mm (lit.¹¹ 95-97 $^{\circ}\text{C}/11$ mm); ^1H NMR (300 MHz, CDCl_3) 5.24 (d, $J = 12$ Hz, 1 H, E), 6.48-6.50 (m, 1 H, E), 6.64 (d, $J = 3.6$ Hz, 1 H, E), 6.95 (d, $J = 12$ Hz, 1 H E), 7.49-7.56 (m, 1 H E & Z) 5.74 (d, $J = 16.2$ Hz, 1 H, Z), 6.52-6.53 (m, 1 H, Z), 7.01 (d, $J = 3.6$ Hz, 1 H, Z), 7.11 (d, $J = 16.2$ Hz, 1 H, Z) ppm; ^{13}C NMR (75 MHz, CDCl_3) 91.14, 112.35, 115.35, 117.21, 134.66, 144.86, 149.78 (E); 93.16, 112.56, 115.38, 118.04, 136.03 145.43 149.98 (Z) ppm.

HCl hydrolysis of 3-(2-furyl)acrylonitrile (11) to γ -ketopimelic acid (12). Based on the procedure of Grundmann and Ruske¹⁴ 3-(2-furyl)acrylonitrile

(0.5 g, 4.2 mmol) was added to conc. HCl (10 mL, 10 mmol) and heated at 55-60 °C for approx. 1h. The reaction mixture was filtered, saturated with NaCl, then extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with saturated NaCl (1 x 40 mL), then dried with MgSO₄. Concentration of the organic layer gave reddish brown solid which was recrystallized from ethyl acetate to give 0.15 g (20.5%) of yellow crystals: mp 130.2-131.2 °C (lit.¹⁷ 143 °C). ¹H NMR (300 MHz, acetone-d₆) 2.54 (t, J = 6.6 Hz, 2 H), 2.74 (t, J = 6.6 Hz, 2 H); ¹³C NMR (75 MHz, acetone-d₆) 27.19, 36.59, 173.41, 205.75 ppm.

3,3,5,5-Tetradeutero-γ-ketopimelic acid (13). Control Experiment

Demonstrating the Exchangeable Protons under the Standard Hydrolysis

Reaction Conditions. γ-Ketopimelic acid (15) (0.1g, 0.6 mmol) was dissolved in conc. DCl (10 mL) and heated at 80 °C for 15-20 min. The reaction mixture was filtered, saturated with solid NaCl, and then extracted with ethyl acetate (3 x 25 mL). After drying with MgSO₄ and evaporating the solvent, the product was recovered quantitatively. ¹H NMR (300 MHz, acetone-d₆) 2.53 (s) ppm.

DCl hydrolysis of 3-(2-Furyl)acrylonitrile (11) to 2,3,3,5,5,6-Hexadeutero-γ ketopimelic acid (14). 3-(2-Furyl)acrylonitrile (0.5 g, 4.2 mmol) in conc. DCl (10 mL) was heated at 70 °C for 1h. After work up the NMR of the product showed hydride transfer to carbon atom 5. ¹H NMR (300 MHz, acetone-d₆) 2.53(s) ppm; ¹³C NMR (75 MHz, acetone-d₆) 27.49, 27.75, 28.01, 173.51, 206.59 ppm.

Furyl Acrylic Acid (15).¹⁵ Freshly distilled furfural (1.7 mL, 0.02 mol), malonic acid (2.1 g, 0.02 mol) and pyridine (1 mL, 0.01 mol) was placed in a 50-mL round-bottomed flask fitted with a reflux condenser. The mixture was heated on a boiling water bath for 2 h, then the reaction mixture was cooled and diluted with water (2 mL). The acid was dissolved by the addition of conc. aqueous ammonia, filtered, then washed with water (3 x 1 mL). The combined filtrates were acidified with an excess of hydrochloric acid (6M). The mixture was cooled by running water and then allowed to stand in an ice bath for 1 h. The furyl acrylic acid was filtered, washed with water (4 x 1 mL) and dried. The yield of colorless needles was 2.5 g. (91-92 %): mp 140-141 °C (lit.¹³ 141 °C) ¹H NMR (300 MHz, acetone-d₆) 6.27 (d, J = 15.9 Hz, 1H), 6.6 (m, 1 H), 6.86 (d, J = 3.3 Hz, 1 H), 7.5 (d, J = 15.9 Hz, 1H) 7.71 (d, J = 3.3 Hz, 1 H) ppm.

HCl hydrolysis of furyl acrylic acid (15) to γ -Ketopimelic Acid (12). Furyl acrylic acid (0.5 g) was dissolved in hot conc. HCl (10 mL) and heated at 55-60 °C for 1h. The reaction mixture was then filtered, saturated with solid NaCl and extracted with ethyl acetate (2 x 25 mL). After drying with MgSO₄ and evaporating the solvent 0.10 g (20%) of the product γ -ketopimelic acid **12** was obtained: ¹H NMR (300 MHz, acetone-d₆) 2.54 (t, J= 6.6 Hz, 2 H) 2.74 (t, J=6.6 Hz, 2 H); ¹³C NMR (75 MHz, acetone-d₆) 27.19, 36.59, 173.41, 205.75 ppm.

β -Nitrostyrene¹⁶. This alkene was prepared by the method of Worall¹⁶ on a 200 mmol scale. The product was yellow crystalline solid: mp 58-59 °C (lit.¹⁶ 57-59 °C); ¹H NMR (300 MHz, acetone-d₆) 7.51-7.56 (m, 1 H), 7.89 (dd, 2 H), 7.96 (d, J = 13.5 Hz, 1 H), 8.09 (d, J = 13.5 Hz, 1H); ¹³C NMR (75 MHz, acetone-d₆) 129.22, 129.45 30.12, 131.90, 137.68, 138.75 ppm.

Hydrolysis of crotonic acid with formaldehyde and hydrochloric acid.

Paraformaldehyde (0.70 g, 23.2 mmol) was dissolved in hot HCl (20 mL). Crotonic acid (1.00 g, 11.6 mmol) was added and the reaction mixture was heated at 60-70 °C for 2 h. The reaction mixture was poured into 20 mL of water and the product was extracted with diethyl ether (2 x 20 mL). After drying the organic layer with MgSO₄ and evaporating the solvent, the product obtained was a liquid. An aliquot of the sample was tested by NMR and the spectrum showed that the product was 3-chlorobutyric acid: ¹H NMR (300 MHz, CDCl₃) 1.58 (d, 3H), 2.8 (m, 2H), 4.42 (m, 1H) ppm.

Hydrolysis of butyric acid with formaldehyde and hydrochloric acid. A Control Experiment. Paraformaldehyde (0.70 g, 23.2 mmol) was dissolved in hot HCl (20 mL). Butyric acid (1.00g, 11.6 mmol) was added and the reaction mixture was heated at 60-70 °C for 2 h. The reaction mixture was poured into 20 mL of water and the product was extracted with diethyl ether (2 x 20 mL). After drying the organic layer with MgSO₄ and evaporating the solvent, butyric acid was obtained quantitatively.

Hydrolysis of crotonic acid with formic acid and hydrochloric acid. Formic acid (2 mL) was added to hydrochloric acid (10 mL) and then crotonic acid (1.00 g, 11.6 mmol) was added to it. It was heated at 60-70 °C for 3 h. After workup and extraction, the product obtained was a liquid. An aliquot of the sample was tested by NMR and the spectrum showed no evidence of reduction of the double bond.

Hydrolysis of cinnamonnitrile with hydrochloric acid and formaldehyde.

Paraformaldehyde (0.26g, 8.7 mmol) was added to hydrochloric acid (10 mL) and then cinnamonnitrile (1.00 g, 7.9 mmol) was added to it. The mixture was heated at 60-70 °C for almost 3 h. After workup and extraction, the product obtained was a white crystalline solid. An aliquot of the sample was tested by NMR and the spectrum showed that the product was a mixture of *cis* and *trans* cinnamic acids.

Hydrolysis of cinnamonnitrile with hydrochloric and formic acid. Formic acid (0.33 g, 8.7 mmol) was added to sulphuric acid (15 mL) and the reaction mixture heated at 70-80 °C. Cinnamonnitrile (1.00 g, 7.9 mmol) was added to the reaction vessel and heating was continued for 2 h. After workup and extraction, the product obtained was solid. An aliquot of the sample was tested by NMR and the spectrum showed a mixture of *cis* and *trans* cinnamic acids.

Hydrolysis of crotononitrile with hydrochloric acid and formaldehyde.

Paraformaldehyde (2.0 g, 67 mmol) was added to hydrochloric acid (10 mL) and the reaction vessel was heated until the paraformaldehyde dissolved. Crotononitrile (0.45 g, 6.7 mmol) was added to the reaction mixture and heated at 60-70 °C for 3 h. After workup and extraction, an aliquot of the sample was tested by NMR and the spectrum showed that the product obtained was crotonic acid and 3-chlorobutyric acid. ¹H NMR (300 MHz, CDCl₃) 1.58 (d, 3H), 2.8 (m, 2H), 4.42 (m, 1H).

Hydrolysis of cinnamic acid with hydrochloric acid and formaldehyde.

Paraformaldehyde (2.0 g, 67 mmol) was added to hydrochloric acid (10 mL)

and the reaction vessel was heated until the paraformaldehyde dissolved. Following addition of cinnamic acid (1.00 g, 6.7 mmol), the reaction mixture was heated at 60-70 °C for 3 h. After workup and extraction the starting material was recovered.

Hydrolysis of β -nitro styrene with formaldehyde and hydrochloric acid.

Paraformaldehyde (1.00 g, 33.5 mmol) was added to hydrochloric acid (10 mL) and the mixture was heated until it completely dissolved. β -Nitrostyrene (0.5 g, 3.4 mmol) was added to the reaction vessel and the heated at 60-70 °C for 2 h. After work up and extraction, the product obtained was a yellow solid and the NMR showed that we had recovered the starting material.

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