



Kinetics of Thiazole Formation Using α -Halo Ketones and Thioamides

PRAJAKTA SHAMRAO SADAVARTE, BHASKAR HARI ZAWARE*
and **SUSHAMA JAYAWANT TAKATE**

Department of Chemistry, New Arts, Commerce and Science College, Ahmednagar, India.

*Corresponding author E-mail: bhaskarzaware@gmail.com

<http://dx.doi.org/10.13005/ojc/380427>

(Received: June 27, 2022; Accepted: August 13, 2022)

ABSTRACT

The current approach involves the kinetic investigation of Thiobenzamide (TB) and cyclohexanone thiosemicarbazone (CTSC) in solution with 3-chloroacetylacetone(3-CAA). The study revealed a second-order rate constant with respect to both reactants, thioamide and an α -halo carbonyl compound. The energy of activation (E_a) was found to be E_a 48.8176kJ/mol/K for thiobenzamide and 33.08692157 kJ/mol/K for Cyclohexanone thiosemicarbazone. The salt effect study showed the formation of ionic species during the reaction. The reactions were studied with respect to changes in dielectric constant using solvent systems like water-ethanol and water-isopropanol.

Keywords: Kinetics, Cyclisation, Thermodynamic parameter, Dielectric constant, Mechanism.

INTRODUCTION

Hantzsch thiazole cyclization is the crucial synthetic route for thiazole-containing compounds which have numerous applications. Thiazoles are found in a variety of natural products, including carboxylase vitamin B1, thiamine pyrophosphate (TPP), and penicillin¹, many of the compounds which are in current clinical use for bacterial infection², allergies³, HIV infections⁴, hypertension⁵, as hypnotic agents⁶, schizophrenia⁷ and pain⁸ and inhibition of bacterial DNA gyrase B9 possess thiazole as part of the structure. Thiazole anchored molecules exhibit antifungal¹⁰, anti-inflammatory¹¹⁻¹², analgesic¹³, anticonvulsant¹⁴, anti-cancer¹⁵⁻¹⁶ and antimicrobial¹⁷⁻¹⁹ properties also.

The current work reports on pH metric measurements of the cyclisation of thioamides and 3-chloroacetylacetone in a water-ethanol system to observe the concentration of H^+ ion in the solution phase.

Available literature shows that so far very less work has been carried out on the kinetics of thiazole formation. We previously used 3-chloroacetylacetone and substituted thioureas to investigate thiazole formation²⁰. The reaction between 3-chloroacetylacetone and thioamides is still to be reported. As it is unexplored for its kinetic aspect, it must be studied for the same. In 1884, Van't Hoff²¹ proposed a method for calculating rates based on the



slope of a concentration versus a time plot.

$$n = \frac{\log\left(\frac{dc}{dt}\right)_I - \log\left(\frac{dc}{dt}\right)_{II}}{\log C_i - \log C_{ii}} \quad (1)$$

The cage model was utilized by Robinowitch²² to improve the collision theory for second-order processes in solution. According to the transition state theory²³, which gives a straightforward way of putting together reaction rates and how the process occurs. According to Eyring and Laidler²⁴, the energy barrier is required for product formation, which provides the activation energy through the development of the activated complex. The energy of activation E_a and preexponential factor-A are computed using the Arrhenius equation in the solution phase reaction as the temperature is varied²⁵.

$$k = A e^{\frac{-E_a}{RT}} \quad (2)$$

It was estimated the activation energy, preexponential factor, activation entropy, and free energy.

$$E_a = \frac{4.576 T_1 T_2 (\log k_2 - \log k_1)}{T_2 - T_1} \quad (3)$$

For bimolecular reaction,

$$E_a = \Delta H^\ddagger + 2RT$$

The solvent binding is shown to restrict the free movement of molecules by negative entropy²⁶. When entropy is lost, an activated complex is generated.

According to the salt effect, when the interacting species are oppositely charged, the rate drops as the ionic strength increases.

$$I = 1/2 \sum c_i z_i^2 \quad (4)$$

Debye and Huckel²⁷ and Bronsted²⁸

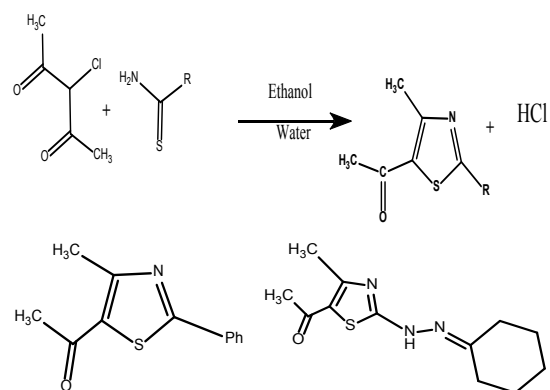
$$\log k/k_0 = 1.02 z_A z_B \sqrt{I} \quad (5)$$

$\log k$ and \sqrt{I} (mol dm^{-3}) A straight line with a slope of $1.02 z_A z_B$ is seen in the graph. The rate-determining phase of the reaction is between oppositely charged species, which has a negative slope^{29,32} and indicates that oppositely

charged species are present in the reaction. The data influence of the dielectric constant is explored by Akerlof³⁰, and the data is used in this study. The dielectric constants for the composition of water-ethanol and water-isopropanol systems were obtained using the supplied standard graph.

Using the double sphere model, Scatchard's³¹ equation is employed for the mixed solvent with variable dielectric constant, according to electrostatic theory. The logarithm of the rate constant plotted against the reciprocal of the dielectric constant yields a linear curve²⁴. It has been observed that there is some variation from linearity at low values of dielectric constants.

$$\ln k = \ln k_0 - \frac{z_A z_B e^2}{4\pi\epsilon\epsilon_0 d_{AB} kT} \quad (6)$$



Scheme 1. Reaction between thioamide with 3-chloroacetyl acetone

MATERIALS AND METHODS

A digital pH meter was used to determine the change in pH with the progress of the reaction. (EQUIPTRAONICS, EQ-614A). All of the reagents employed were analytical reagents. Glass distilled water and pure alcohol were used to perform the experiment.

EXPERIMENTAL

Four different parts were carried out for the kinetic study of the reaction.

Effect of concentration

To evaluate the order of reaction in the case of α -halo ketone, the reaction was carried out with various concentrations of α -halo ketone

while maintaining the concentration of thioamide constant (0.05N) at 300K. By plotting a graph of H⁺ concentration versus time in minutes, the dc/dt values were calculated. By drawing a tangent at a specific time, the values of dc/dt were computed, as well as the sequence of reactions for each reactant. The slope of the log dc/dt graph versus and found to be nearly one. With respect to 3-chloroacetyl acetone, this observation shows that the reaction is first order.

Effect of variation of temperature

The reaction between two different substituted thioamides and 3-chloroacetyl acetone was studied kinetically using equal concentrations at 300K, 303K, 308K, 3013K, 318K, and 323K. The activation energy (E_a) reactions were determined by plotting 1/T vs log k.

Effect of salt addition

The reaction between two distinct

substituted thioamides and 3-chloroacetyl acetone was studied kinetically using equal amounts of sodium chloride and lithium chloride at 300K. The slope of the plot of $\sqrt{\mu}$ versus log k is negative.

Effect of solvent

The reaction between two distinct substituted thioamides and 3-chloroacetyl acetone was studied kinetically at 300K utilizing the Water-Ethanol and Water-Isopropyl alcohol systems at equal concentrations. By using the double sphere mechanism, plotting 1/T vs log k gives a negative value, which indicates the d_{AB} distance between two ions.

Table 1: Order of the reaction with respect to one reactant

Reactants	Order	Reactants	Order
TB change	1.1471	CTSC change	1.10872
3-CAA change	0.5339	3-CAA change	1.17052

Table 2: Temperature effect and thermodynamic parameters: Thioamide reacts with 3-chloroacetylacetone

Temperature(°C)	EakJ/mol/K	ΔH^* kJ/mol/K	ΔS^* kJ/mol	ΔG^* kJ/mol
Thiobenzamide	48.8176	43.8292	-0.1282	82.3009
Cyclohexanone	33.0869	28.0985	-0.1635	77.1645
Thiosemicarbazone				

Table 3: Rate constants for salt effect (dm³mol⁻¹s⁻¹)

Concentration/Salt effect	0.1N	0.2N	0.3N	0.4N
TB and 3CAA (NaCl)	5.34X10 ⁻³	5.09X10 ⁻³	4.86X10 ⁻³	4.12X10 ⁻³
TB and 3CAA (LiCl)	4.61X10 ⁻³	3.76X10 ⁻³	3.53X10 ⁻³	3.37X10 ⁻³
CTSC and 3CAA (NaCl)	2.85 X10 ⁻²	2.12 X10 ⁻²	2.02 X10 ⁻²	1.82 X10 ⁻²
CTSC and 3CAA (LiCl)	1.90 X10 ⁻²	1.74 X10 ⁻²	1.58 X10 ⁻²	1.39 X10 ⁻²

Table 4: Rate constant in the water-ethanol system (dm³mol⁻¹s⁻¹)

TB and 3-CAA reaction	Rate (Water-Ethanol system)	Rate (Water-Isopropanol system)
85-15	1.73 X10 ⁻³	3.31 X10 ⁻³
75-25	1.87 X10 ⁻³	3.46 X10 ⁻³
65-35	2.27 X10 ⁻³	3.93 X10 ⁻³
55-45	2.79 X10 ⁻³	4.33 X10 ⁻³

Table 5: Rate constant in the water-Isopropanol system (dm³mol⁻¹s⁻¹)

CTSC and 3-CAA reaction	Rate (Water-Ethanol system)	Rate (Water-Isopropanol system)
85-15	1.55 X10 ⁻²	6.38 X10 ⁻⁴
75-25	2.06 X10 ⁻²	7.60 X10 ⁻⁴
65-35	2.19 X10 ⁻²	9.88 X10 ⁻⁴
55-45	2.34 X10 ⁻²	1.37 X10 ⁻³

General mechanism and rate expression are proposed



S_1 - 3-Chloroacetylacetone

S_2 - Thioamides

$$\text{Rate} = k_1[S_1][S_2] - k_{-1}[\text{Intermediate}]$$

On applying steady state approximation

$$\frac{d}{dt}[\text{Intermediate}] = 0 = k_1[S_1][S_2] - k_{-1}[\text{Intermediate}] - k_2[\text{Intermediate}]$$

$$[\text{Intermediate}] = \frac{k_1[S_1][S_2]}{k_{-1} + k_2}$$

Substituting the value of [Intermediate] in the equation

$$\text{Rate} = k_1[S_1][S_2] - \frac{k_{-1}k_1[S_1][S_2]}{k_{-1} + k_2}$$

$$\text{Rate} = \left\{ k_1 - \frac{k_{-1}k_1}{k_{-1} + k_2} \right\} [S_1][S_2]$$

Fig. 1. Rate constant for the second-order reaction between α -halo ketone with thioamides

RESULT AND DISCUSSIONS

Using Van't Hoff's differential method, the plot of $\log (dc/dt)$ against \log 3-chloroacetylacetone and \log thioamide is a straight line with a slope of nearly one with respect to both, and the stoichiometric study suggested that one mole of thioamide reacts with one mole of 3-chloroacetylacetone. (Table 1, Fig. 1, 2). The reaction takes place in a two-step sequence. As the reaction is performed at moderate temperatures and no free radical initiators are used, there is no possibility of free radical formation. The second-order rate constants were investigated at various temperatures. Other thermodynamic parameters were derived by studying the reaction at various temperatures. The energy of activation (E_a) was established by producing a graph of $\log k$ versus $1/T$. (Table 2, Fig. 3, 4). The reaction's entropy of activation (S^*) is negative, indicating that the transition state is inflexible. When (H^*) is negative, the reaction is exothermic. The reaction is exothermic when (H^*) is negative. The activation entropy (S^*) is negative, indicating that less stable noncyclic reactants transform into stable cyclic products. The activation entropy has a negative value, indicating stiffness in the transition state. The reaction could happen between ions with the same charge. The nucleophile and electrophile

moieties are involved in the reaction, as seen by the negative slope of $1/T$ versus $\log k$. (Table 3, Fig. 5, 6). The dAB is obtained by plotting the $1/T$ vs $\log k$ values (distance between two ions by double sphere mechanism). The reaction is faster in the water-isopropyl alcohol system than in the water-ethanol system. (Table 4,5 Fig. 7, 8, 9). According to the kinetic theory of collision, if the ions are of opposite sign, the frequency will increase due to the attraction force.

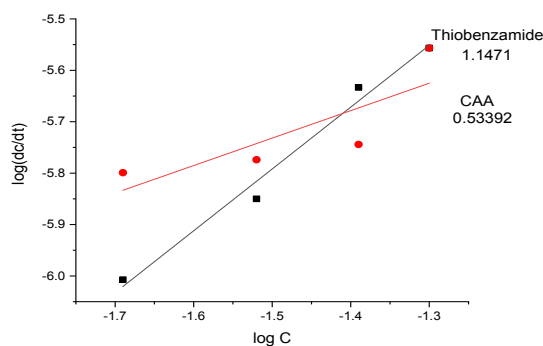


Fig. 2. Order of the reaction between Thiobenzamide and 3-Chloroacetylacetone

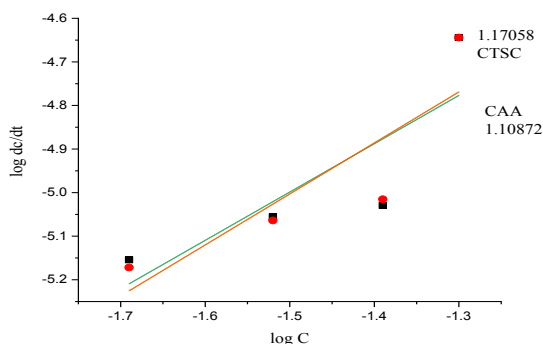


Fig. 3. Order of the reaction between 3-Chloroacetylacetone and Cyclohexanone thiosemicarbazone

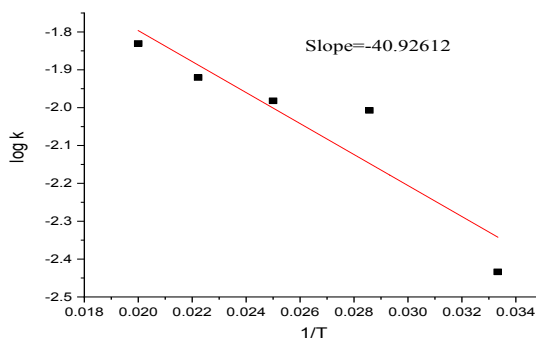


Fig. 4. Temperature change of the reaction between Thiobenzamide and 3-Chloroacetylacetone

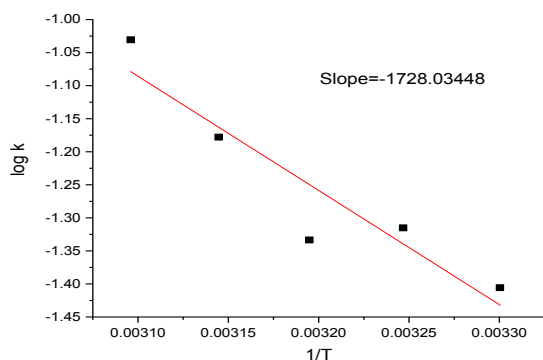


Fig. 5. Temperature change of the reaction between 3-Chloro-acetylacetone and Cyclohexanone thiosemicarbazone

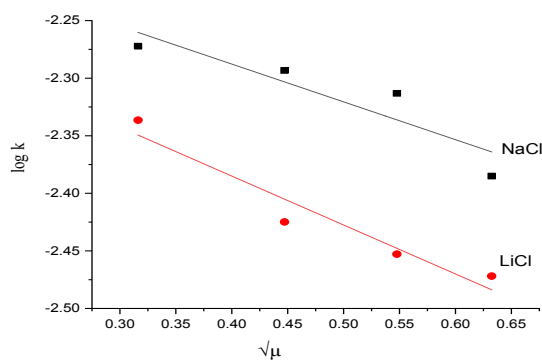


Fig. 6. Salt effect on Thiobenzamide and 3-Chloroacetylacetone

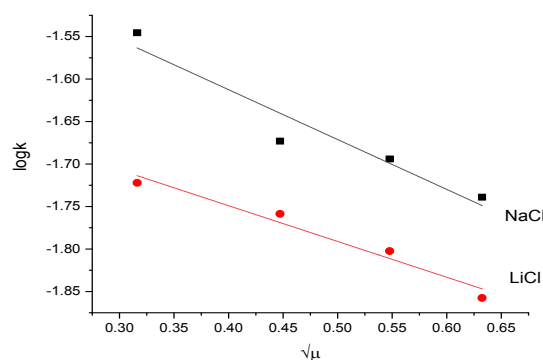


Fig. 7. Salt effect on 3-Chloroacetylacetone and Cyclohexanone thiosemicarbazone

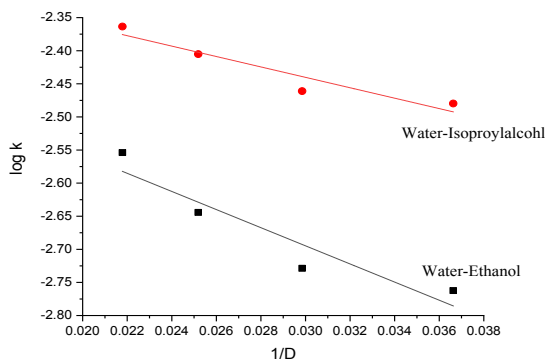


Fig. 8. Solvent effect on Thiobenzamide and 3-Chloroacetylacetone

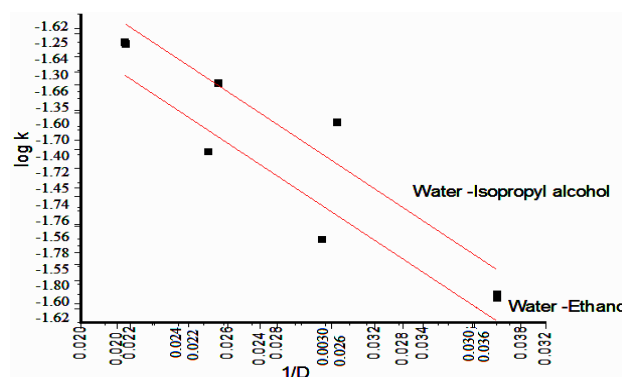


Fig. 9. Solvent effect on 3-Chloroacetylacetone and Cyclohexanone thiosemicarbazone

CONCLUSION

- Using Van't Hoff's differential approach, the reaction between 3-chloroacetylacetone and thioamides is kinetically examined to establish second-order rate constants.
- The second-order rate of the reaction is also shown by the rate law.
- Rate of the reaction is directly proportional to temperature. At lower temperature reaction

rate will be slowed down.

- Negative entropies cause the open-chain compounds to form a cyclic molecule. It is possible to have nucleophilic addition and addition-elimination processes.
- There is a reaction between oppositely charged moieties such as nucleophile and electrophile.
- As the dielectric constant rises, the rate rises as well. In comparison to the ethanol-water system, the isopropyl alcohol-water system

has a high-rate constant.

V. P. Samaj's, Ahmednagar (M.S.) authorities for their assistance and research facilities.

ACKNOWLEDGEMENT

They expressed gratitude to the A. J. M.

Conflict of interest

There is no conflict of interest.

REFERENCES

- Karam, N. H.; Tomma, J. H.; Al-Dujaili, A. H., *Chem. Mater. Res.*, **2013**, 3(9), 162–171.
- Sharma, R. N.; Xavier, F. P.; Vasu, K. K.; Chaturvedi, S. C.; Pancholi, S. S., *J. Enzyme Inhib. Med. Chem.*, **2009**, 24, 890–897.
- Haragave, K. D.; Hess, F. K.; Oliver, J. T., *J. Med. Chem.*, **1983**, 26(8), 1158–1163.
- Bell, F. W.; Cantrell, A. S.; Hoegberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., *J. Med. Chem.*, **1995**, 38, 4929–4936.
- Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I., *J. Med. Chem.*, **1992**, 35, 2562–2572.
- Ergenç, N.; Çapan, G.; Günay, N.S.; Özkirimli, S.; Güngör, M.; Özbey, S.; Kendi, E. *Arch. Pharm. Pharm. Med. Chem.*, **1999**, 332, 343–347.
- Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Teclé, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzer, L. T.; Pugsley, T. A., *J. Med. Chem.*, **1990**, 33, 311–317.
- Carter, J. S.; Kramer, S.; Talley, J. J.; Penning, T.; Collins, P.; Graneto, M. J.; Seibert, K.; Koboldt, C. M.; Masferrer, J.; Zweifel, B., *Bioorg. Med. Chem. Lett.*, **1999**, 9, 1171–1174.
- Rudolph, J.; Theis, H.; Hanke, R.; Endermann, R.; Johannsen, L.; Geschke, F. U., *J. Med. Chem.*, **2001**, 44, 619–626.
- Lino, C. I.; Gonçalves de Souza, I.; Borelli, B. M.; Silvério Matos, T. T.; Santos Teixeira, I. N.; Ramos, J. P.; Maria de Souza Fagundes, E.; de Oliveira Fernandes, P.; Maltarollo, V. G.; Johann, S.; de Oliveira, R. B., *Eur. J. Med. Chem.*, **2018**, 151, 248–260.
- Sinha, S.; Doble, M.; Manju, S. L., *Eur. J. Med. Chem.*, **2018**, 158, 34–50.
- Kamble, R. D.; Meshram, R. J.; Hese, S. V.; More, R. A.; Kamble, S. S.; Gacche, R. N.; Dawane, B. S., *Comput. Biol. Chem.*, **2016**, 61, 86–96.
- Pember, S. O., Mejia, G. L., Price, T. J. & Pasteris, R. J., *Bioorg. Med. Chem. Lett.*, **2016**, 26, 2965–2973.
- Amin, K. M.; Rahman, A. D. E.; Al-Eryani, Y. A., *Bioorg. Med. Chem.*, **2008**, 16, 5377–3588.
- Wang, Y.; Wu, C.; Zhang, Q.; Shan, Y.; Gu, W.; Wang, S., *Bioorg. Chem.*, **2019**, 84, 468–477.
- da Santana, T. I.; Barbosa, M. O.; Gomes, P. A. T. M.; da Cruz, A. C. N.; da Silva, T. G.; Leite, A. C. L., *Eur. J. Med. Chem.*, **2018**, 144, 874–886.
- Reddy, G. M.; Garcia, J. R.; Reddy, V. H.; de Andrade, A. M.; Camilo, A.; Pontes R., Renan A.; de Lazaro, S. R., *Eur. J. Med. Chem.*, **2016**, 123, 508–513.
- Cushman, M.S.; Seleem, M.; Mayhoub, A. S., United States Patent No.: US 9, 801, 861 B2, **2017**.
- Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M., *Expert Opin. Ther. Patents.*, **2014**, 24, 201–216.
- Zaware, B. H.; Mane, R. A.; Kuchekar, S. R., *J. Chem. Pharma. Res.*, **2009**, 1(1), 276.
- Van't Hoff, J. H., Multer compony, Amsterdam., **1984**.
- Rabinovitch, E., *Trans. Faraday Soc.*, **1937**, 33, 1225.
- Laidler, K. J.; King, M. C., *J. Phys. Chem.*, **1983**, 87, 2657.
- Laidler, K. J.; Eyring, H., *Ann. N. Y. Acad. of Sciences.*, **1940**, 39, 303.
- Arrhenius, S., *J. Phys. Chem.*, **1889**, 4, 226.
- Glassstone, S., *J. Chem. Soc.*, **1936**, 723.
- Laidler, K. J. *Chem. Kinetic.*, **2009**, 195, 3rd ed.
- Debye, P. J. W. and Huckel, E., *Phys. Z.*, **1923**, 24(185), 305.
- Bronsted, J. N.; La Mer, V. K., *J. Am. Chem. Soc.*, **1924**, 46, 555.
- Jonnalagadda, S. B.; Gollapalli, N. R., *J. Chem. Edu.*, **2000**, 77, 4.
- Akerlof, G., *J. Am. Chem. Soc.*, **1932**, 54, 4125.
- Scatchard, G., *Chem. Rev.* **1932**, 10, 229.
- Stokes, R. H.; Robinson, R. A., *J. Am. Chem. Soc.*, **1948**, 70, 1870.