**Acknowledgment.** We thank the National Science Council (ROC) for financial support.

---

# Oxidative Decarboxylation of Alcohol Hemiacetals of $\alpha$-Keto Carboxylic Acids with *N*-Iodosuccinimide

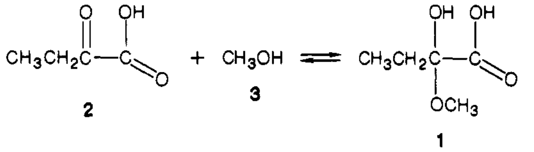
Thomas R. Beebe,* Ruth Baldridge, Mark Beard, Denette Cooke, Isabelle DeFays, Vivian Hensley, Dat Hua, Jia-Cheng Lao, Doug McMillen, Deborah Morris, Robert Noe, Ervin O'Bryan, Clary Spielberger, Matthew Stolte, and Jerome Waller, Jr.

*Department of Chemistry, Berea College, Berea, Kentucky 40404*

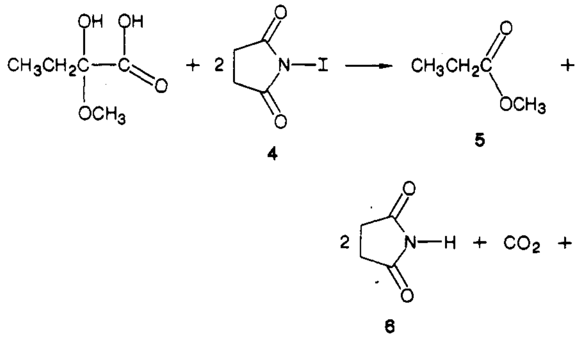
*Received November 17, 1986*

Recently,[1] we found that $\alpha$-hydroxy carboxylic acids were easily decarboxylated with *N*-iodosuccinimide (NIS). At this time, we report that the methyl and ethyl alcohol hemiacetals of $\alpha$-keto carboxylic acids also give good yields of bond-cleavage products when treated with NIS. Similar oxidative cleavage of $\alpha$-keto carboxylic acid hemiacetals using lead tetracetate was observed by Baer,[2] although the pathways are undoubtably different. Both NIS and lead tetraacetate convert hemiacetals of $\alpha$-keto carboxylic acids to esters with the loss of carbon dioxide.

This new reaction with NIS can be illustrated by using the methyl alcohol hemiacetal **1** of $\alpha$-ketobutyric acid (**2**). When the acid **2** and methyl alcohol (**3**) (20 mol excess) in benzene was treated with NIS (**4**), good yields of methyl propionate (**5**) could be obtained by using three different sets of reaction conditions: (1) heating the reaction mixture in the dark (probable radical pathway), (2) irradiating the reaction mixture (probable radical pathway), and (3) stirring the reaction mixture in the dark at ambient temperatures for long time periods (probable pericyclic decomposition pathway for the hemiacetal hypoiodite). The stoichiometry shown in eq 1 and 2 is supported by good yields of iodine and succinimide (**6**). The carbon dioxide product was determined by running the reaction on a vacuum rack. The carbon dioxide filled a gas-collecting bulb, and the molecular weight of the collected gas was 43.8. Mass spectrometer analysis confirmed the presence of $CO_2$ as a product in the NIS oxidation of the hemiacetals.

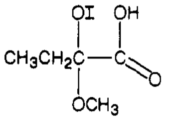


(1)

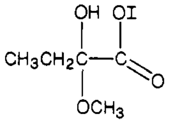


(2)

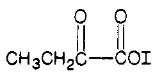
Three hypoiodite intermediate products are possible when the $\alpha$-keto carboxylic acids react with NIS. Either the hemiacetal hypoiodite **7** or the acyl hypoiodites **8** and **9** could be intermediates. There is good evidence[3,4] for the formation of alkyl hypoiodites from the reaction of alcohols and NIS and the subsequent decomposition of the alkyl hypoiodites with heat or light to produce alkoxy radicals. The chemistry of the reaction of simple carboxylic acids with NIS to form acyl hypoiodites has not been established. Quantitative yields[5] of *N*-iodosuccinimide (**4**) and acetic acid (**10**) are produced when acetyl hypoiodite (**11**) and succinimide (**6**) are mixed (eq 3), which indicates that little acyl hypoiodite is present when succinimide is available to be iodinated. Radical decomposition of the acyl hypoiodite **9** would involve the formation of an acyl iodide intermediate which would react with the alcohol present to produce the ester and HI.



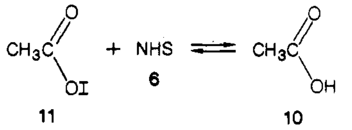
**7**



**8**



**9**

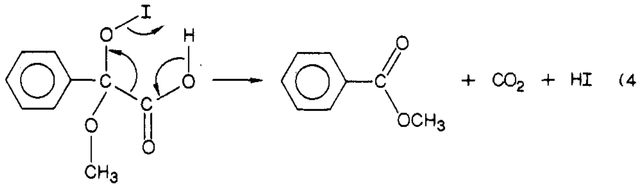


(3)

Intermediate methyl ester or dimethyl ketal products of the $\alpha$-keto carboxylic acid were ruled out because of the speed of the light- and heat-catalyzed reactions. Without the presence of strong mineral acids, esters and ketals are formed very slowly when alcohols and carboxylic acids or alcohols and ketones, respectively, are heated together.

The methyl and ethyl alcohol hemiacetals of three $\alpha$-keto carboxylic acids ($\alpha$-ketobutyric acid, pyruvic acid, and benzoylformic acid) were subjected to NIS oxidative decarboxylation. Table I outlines these oxidative cleavages.

Product formation was fastest for the reactions that were heated and irradiated. We believe that the decomposition of the hemiacetal hypoiodite with irradiation follows a radical process to produce the observed products. A concerted, pericyclic pathway (eq 4) is possible for the decarboxylation of the hypoiodite **12** in the room temperature, dark reactions. The methyl alcohol hemiacetal hypoiodite of benzoylformic acid is shown in eq 4. The production of $I_2$ and NIS in the dark, ambient temperature reactions occurs when the HI decomposes the NIS, a reaction seen in all NIS oxidations where HI is produced.



(4)

The stoichiometry of eq 1 indicates a one-to-one mole ratio of keto acid and alcohol is needed to form the hemiacetals. To increase the chance of hemiacetal formation

---

[1] Beebe, T. R.; Adkins, R. L.; Belcher, A. I.; Choy, T.; Fuller, A. E.; Morgan, V. L.; Sencherey, B. B.; Russell, L. J.; Yates, S. W. *J. Org. Chem.* **1982**, *47*, 3006.

[2] Baer, E. *J. Am. Chem. Soc.* **1940**, *62*, 1597.

[3] Beebe, T. R.; Adkins, M.; Kwok, P.; Roehm, R. *J. Org. Chem.* **1972**, *37*, 4220. Beebe, T. R.; Lin, A. L.; Miller, R. D. *Ibid.* **1974**, *39*, 722.

[4] Meystre, C.; Heusler, K.; Kalvoda, J.; Wieland, P.; Anner, G.; Wettstein, A. *Experientia* **1961**, *17*, 475. Heusler, K.; Kalvoda, J.; Meystre, C.; Anner, G.; Wettstein, A. *Helv. Chim. Acta* **1962**, *45*, 2162. Heusler, K.; Kalvoda, J. *Angew Chem.* **1964**, *76*, 518.

[5] Beebe, T. R.; Wolfe, J. W. *J. Org. Chem.* **1970**, *35*, 2057.

0022-3263/87/1952-3165$01.50/0

**Table I**

| α-keto acid | alcohol | product | reactn conditions[a] | solvent | yield range, % |
|---|---|---|---|---|---|
| α-ketobutyric accid | methanol | methyl propionate | light, heat | benzene | 76-81 |
| | | | dark, heat | benzene | 68-73 |
| | | | dark, ambient | acetonitrile | 63-75 |
| α-ketobutyric acid | ethanol | ethyl propionate | light, heat | benzene | 81-86 |
| | | | dark, heat | benzene | 68-81 |
| | | | dark, ambient | acetonitrile | 53-59 |
| pyruvic acid | methanol | methyl acetate | light, heat | benzene | 60-64 |
| | | | dark, heat | benzene | 59-63 |
| | | | dark, heat | acetonitrile | 59-71 |
| | | | dark, ambient | acetonitrile | 57-64 |
| pyruvic acid | ethanol | ethyl acetate | light, heat | benzene | 63-72 |
| | | | dark, heat | benzene | 67-77 |
| | | | dark, heat | acetonitrile | 61-78 |
| | | | dark, ambient | acetonitrile | 73-78 |
| benzoylformic acid | methanol | methyl benzoate | light, heat | benzene | 71-78 |
| | | | dark, heat | benzene | 79-94 |
| | | | dark, ambient | benzene | 79-85 |
| benzoylformic acid | ethanol | ethyl benzoate | light, heat | benzene | 81-86 |
| | | | dark, heat | benzene | 78-81 |
| | | | dark, ambient | benzene | 73-88 |

[a] Heat indicates the reflux temperature of the solvent/alcohol mixtures.

an excess of alcohol (from 4 to 20 mol excess) was used. No alcohol oxidation products were found.

## Experimental Section

Analyses were performed on Varian Models 3400 and 3700 VPC's and a Hewlett-Packard 5700A VPC. Liquid chemicals used in the reaction mixtures and the standard VPC mixtures all had greater than 99.5% purity as determined on a gas chromatograph. The benzene and the acetonitrile solvents were spectroscopically pure and were used as purchased. VPC analyses were done on 6 ft × 0.25 in. copper columns of 10% SE-30, 7% SE-30, 3% Carbowax 20M, and 10% Carbowax 20M. The *N*-iodosuccinimide was determined to have 98.0-99.5% active iodine and was used as purchased. Irradiation of reaction mixtures was effected with a GE Projector Spot 150-W, 130-V tungsten lamp.

**Oxidative Decarboxylation of the Methyl Alcohol Hemiacetal of α-Ketobutyric Acid with *N*-Iodosuccinimide and Irradiation.** A 5-mL solution of 0.113 g (1.30 mmol) of α-ketobutyric acid, 0.166 g (5.20 mmol) of methyl alcohol, and 0.124 (1.10 mmol) of chlorobenzene (internal standard) in benzene was added to 0.644 g (2.86 mmol) of NIS contained in a 10-mL flask. A condenser with a drying tube was attached to the flask. The mixture was stirred and irradiated. Reaction times and VPC percentage yields of methyl propionate were as follows: 12 min (49%), 37 min (75%), 2.5 h (81%), 3.5 h (81%). Elemental iodine determination gave 0.979 mmol (75%). Succinimide was recovered in 86% yield. No methyl formate, a possible oxidation product of the methyl alcohol hemiacetal of formaldehyde, was found.

**Oxidative Decarboxylation of the Ethyl Alcohol Hemiacetal of α-Ketobutyric Acid with NIS in the Dark with Heat.** A 5-mL solution of 0.104 g (1.02 mmol) of α-ketobutyric acid, 0.202 g (4.39 mmol) of ethyl alcohol, and 0.114 g (1.01 mmol) of chlorobenzene (internal standard) in benzene was added to 0.459 g (2.04 mmol) of NIS contained in a 10-mL flask. The condenser was protected with a $CaCl_2$ drying tube. The flask was wrapped in Al foil and the mixture heated at reflux. Reaction times and VPC percentage yields of ethyl propionate were as follows: 15 min (70%), 45 min (78%), 1.25 h (79%), 2 h (81%), 3 h (80%). Titration for elemental iodine gave 87% recovery. Succinimide was recovered in 67% yield. No ethyl acetate, a possible oxidation product of the ethyl alcohol hemiacetal of acetaldehyde, was found.

**Oxidative Decarboxylation of the Methyl Alcohol Hemiacetal of Benzoylformic Acid with NIS in the Dark with Heat.** A 5-mL solution of 0.153 g (1.02 mmol) of benzoylformic acid, 0.641 g (20.0 mmol) of methyl alcohol, and 0.120 g (1.06 mmol) of chlorobenzene (internal standard) in benzene was added to 0.466 g (2.07 mmol) of NIS in a 10-mL round-bottomed flask. The condenser was topped with a $CaCl_2$ drying tube. The flask was wrapped in Al foil. The mixture was stirred. Reaction times and VPC percentage yields of methyl benzoate are given: 1 h (49%), 3 h (67%), 4.75 h (71%), 6 h (75%), 7.5 h (79%). Iodine was found with a yield of 84%. Succinimide was recovered in 53% yield.

**Oxidative Decarboxylation of the Methyl Alcohol Hemiacetal of Benzoylformic Acid with NIS in the Dark at Ambient Temperatures.** A 5-mL solution of 0.157 g (1.05 mmol) of benzoylformic acid, 0.641 g (20.0 mmol) of methyl alcohol, and 0.120 g (1.06 mmol) of chlorobenzene (internal standard) in benzene was added to 0.490 g (2.18 mmol) of NIS contained in a 10-mL flask. The condenser was protected with a $CaCl_2$ drying tube. The flask was wrapped with Al foil and the mixture stirred. Reaction times and percentage yields of methyl benzoate are given: 2 h (17%), 21 h (37%), 84 h (80%), 122 h (85%), 144 h (85%). Titration for iodine gave 1.09 mmol (104%). Succinimide (1.74 mmol) was recovered in 84% yield.

**Iodine Determination.** The iodine produced in the oxidations was determined by adding the reaction mixtures to 25 mL of a 1:1 mixture of acetic acid and water. Several drops of concentrated HCl were added, and the iodine was titrated with a standardized solution of thiosulfate.

**Succinimide Determination.** Succinimide was recovered by cooling the reaction mixtures and filtering the precipitated solid.

**Acknowledgment.** We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research. We also thank the Department of Chemistry of the University of Kentucky for mass spectrometry data.

**Registry No.** NIS, 516-12-1; α-ketobutyric acid, 600-18-0; pyruvic acid, 127-17-3; benzoylformic acid, 611-73-4; methyl propionate, 554-12-1; ethyl propionate, 105-37-3; methyl acetate, 79-20-9; ethyl acetate, 141-78-6; methyl benzoate, 93-58-3; ethyl benzoate, 93-89-0.

---

# An Improved Method for the Decyanation of N,N-Disubstituted Cyanamides

Jerry W. Misner

*Lilly Research Laboratories, Eli Lilly and Company,*
*Indianapolis, Indiana 46285*

*Received February 23, 1987*

The decyanation of N,N-disubstituted cyanamides to secondary amines is a well-known method[1] that is used extensively, particularly in conjunction with the von Braun degradation for the N-dealkylation of alkaloids. Typically,

---

[1] Vliet, E. B. In *Organic Syntheses*, 2nd ed.; Gilman, H., Blatt, A. H., Eds.; Wiley: New York, 1941; Collect. Vol. I, pp 201-202.