N-Iodosuccinimide Mediated Oxidative Decarboxylation of Carboxylic Acids

Presented to the faculty of Lycoming College in partial fulfillment of the requirements for graduation with Departmental Honors in Chemistry

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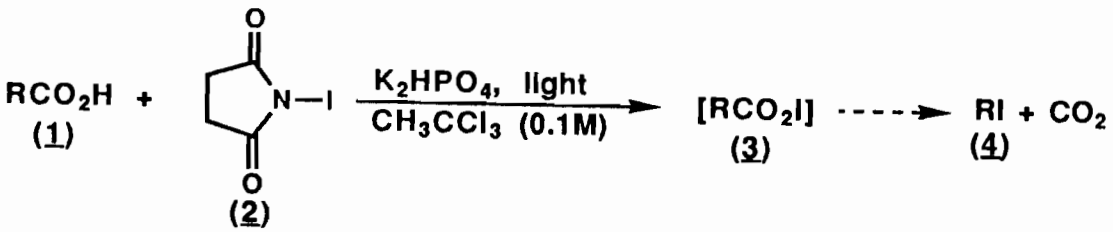
ABSTRACT

Functional group transformation and manipulation of the carbon skeleton of organic molecules are two of the main challenges which confront synthetic chemists. The aim of this research was to optimize and examine the scope of the N-iodosuccinimide (2) mediated oxidative decarboxylation of carboxylic acids (1). The reaction is believed to occur by photolytic decomposition of an intermediate acyl hypoiodite (3).



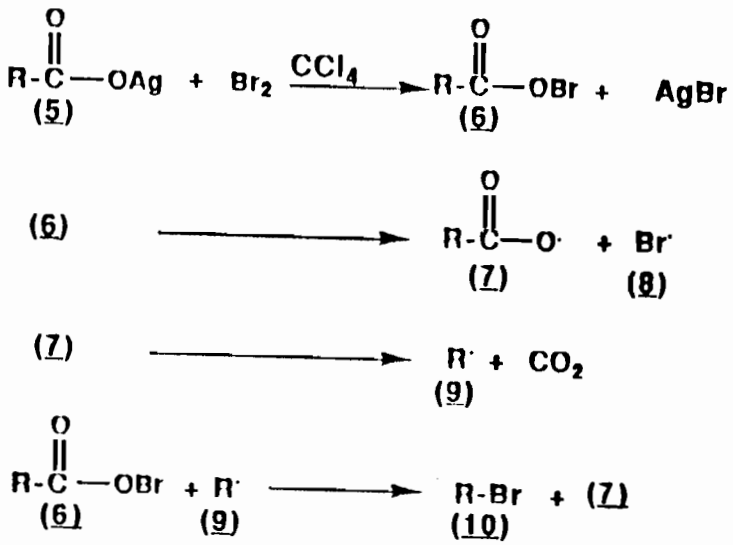
Also, in situ nucleophilic displacement of the incipient alkyl iodide to the corresponding methyl ether was examined.

INTRODUCTION

Synthetic chemists are always searching for novel methodologies for functional group transformations. We examined the transformation of carboxylic acids to alkyl iodides and carbon dioxide. Several methods by which this can be accomplished have already been reported in the literature.

The most common reaction used to convert carboxylic acids to alkyl halides is the Hunsdiecker reaction outlined in Scheme 1.

SCHEME 1



The silver salt of the carboxylic acid (5) is heated with carbon tetrachloride and bromine. The resulting hypobromite (6) is homolytically and photolytically cleaved to generate a carboxyl radical and a bromine radical (7 and 8). The carboxyl radical

then decarboxylates to make carbon dioxide and the corresponding alkyl radical (9). This radical abstracts a bromine atom from the hypobromite to regenerate a carboxyl radical (7) and an alkyl bromide (10).[1]

Kochi prepared alkyl chlorides (11) by decarboxylation of carboxylic acids (1) with lead acetate and lithium chloride in refluxing benzene.[2]

$$(1) \xrightarrow[\text{refluxing benzene}]{Pb(OAc)_4,\ LiCl} R\text{-}Cl\ (11) + CO_2$$

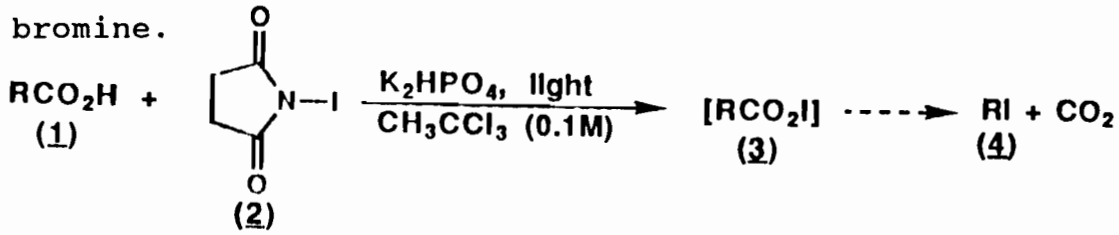
This reaction is especially useful in preparing secondary and tertiary alkyl chlorides because the Hunsdiecker reaction and it's modified version by Cristol and Firth give low yields for these alkyl chlorides.[2] Grob improved this reaction by replacing lithium chloride with N-chlorosuccinimide (NCS) as a chlorine donor and replacing benzene with a 5:1 mixture of dimethylformamide (DMF) and acetic acid. By doing this, he was able to run the reaction at 40-55°C instead of refluxing the reaction, allowing heat sensitive chlorides to be formed without decomposition.[3]

$$(1) \xrightarrow[\text{DMF/acetic acid(5:1)}]{NCS,\ Pb(OAc)_4\ 40\text{-}55^\circ C} R\text{-}Cl\ (11) + CO_2$$

INTRODUCTION

Our idea came from the Hunsdiecker equation except N-iodosuccinimide is used to produce the initial hypohalite instead

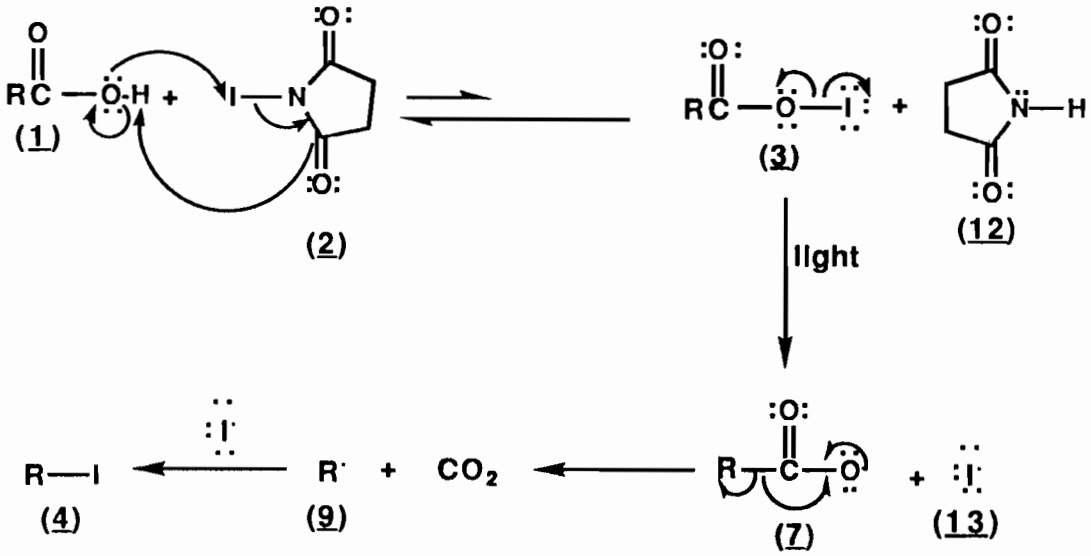
of bromine.



McDonald took the carboxylic acid (1) and treated it with N-iodosuccinimide (NIS), light to homolytically cleave the hypoiodite, and chloroform at 60°C (using the heat produced by the light as the heat source). Gas chromotography indicated that 60% alkyl iodide (4) was formed.

The reaction is thought to proceed as noted in SCHEME 2.

SCHEME 2

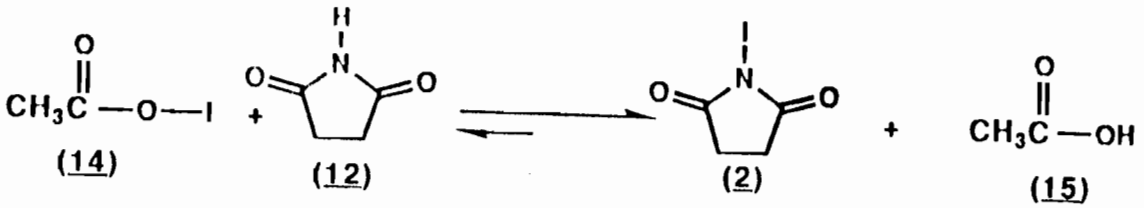


The carboxylic acid (1) is oxidized by NIS (2) to form the corresponding acyl hypoiodite (3) and succinimide (12). The acyl hypoiodite is homolytically cleaved to generate a carboxyl radical and an iodine radical (7 and 13). Then the carboxyl

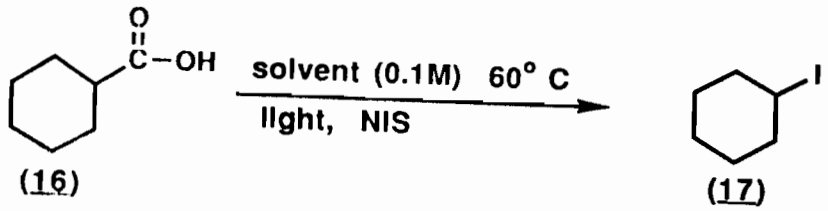
radical homolytically cleaves to form an alkyl radical (9) and carbon dioxide. The resulting alkyl radical then reacts with the iodide radical, hypoiodite, or I_2 (formed during the reaction) to form the corresponding alkyl iodide (4).

RESULTS AND DISCUSSION

The main goal of this research was to first optimize this reaction and then to examine the scope and limitations of the reaction. The biggest problem in achieving a good yield of alkyl iodide is undoubtedly the unfavorable equilibrium associated with the oxidation of the carboxylic acid using NIS. In fact Beebe has used acetyl hypoiodite (14) to oxidize succinimide (12) to NIS (2) and acetic acid (15).[4]



The steps which follow the initial formation of the acyl hypoiodite should all be essentially irreversible. The first step is a polar reaction, thus the rate of formation of acyl hypoiodite should be enhanced by using a polar solvent. Thus the first step in optimization of this reaction was an attempt to find more polar solvents, which were selected based upon their dielectric constant and similar to chloroform. Solvents with a higher dielectric constant will aid the polar first step of the mechanism (See Table 1). The carboxylic acid used to optimize this reaction was cyclohexanecarboxylic acid (16).



(16) (17)

TABLE 1

SOLVENT	**MAX YIELD	HOURS	DIELECTRIC CONSTANT
Benzene	35%	10	2.28
Hexane	38%	20	2.02
Chloroform	60%	3	4.81
Acetonitrile	36%	4	3.44
Dimethylformamide	0%	8	36.7
Carbon tetrachloride	32%	4	2.24
*1,1,1-Trichloroethane	60%	5	7.6

* reaction ran by Michael Justice all others ran by Dr. McDonald
**G C yields (not isolated)

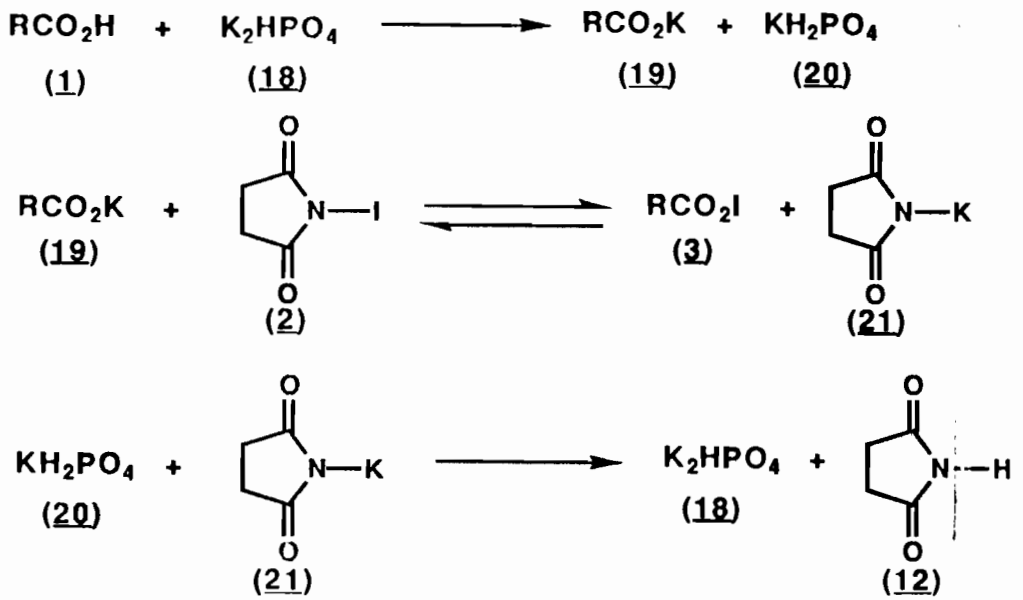
As can be seen in Table 1, only one 1,1,1-trichloroethane, besides chloroform gave any appreciable yields of product. Chloroform was later eliminated as a solvent possiblity and 1,1,1-trichloroethane seemed to be the most optimal solvent to use. Chloroform was discontinued as the reaction solvent, because it was thought to be homolytically cleaving to make various radicals and it was also reacting with the alkyl radical

(9).

Even though 1,1,1-trichloroethane was picked as the optimal solvent, the final yield of the reaction was still only 60.0%. The problem was that we could not detect the starting material by TLC or gas chromotography analysis. This problem was solved when AT-1000 packing material for the GC column was purchased. This packing material was nonpolar enough so that the reaction could now be monitored by GC analysis, meaning that the starting material and the product could now be detected by gas chromatography. It now became obvious where the problem was located. The reaction was stopping before all the carboxylic acid had been consumed. To remedy this three more equivalents of NIS were added during the reaction, 2 more equivalents when yield of the cyclohexyl iodide showed a rapid increase and 1 more equivalent when the yield of cyclohexyl iodide showed a rapid increase again. The exact time that the NIS is added during each reaction is always a little different due to the fact that it is a heterogeneous mixture.

The next way this reaction was optimized was to use the conjugate base of the carboxylic acid in an attempt make the equilibrium more favorable in the first step of the reaction mechanism. By deprotonating the carboxylic acid, it will become a better nucleophile, thus making the reaction more facile. Out of all the bases that were tried dipotassium hydrogen phosphate worked out most elegantly (see Scheme 3).

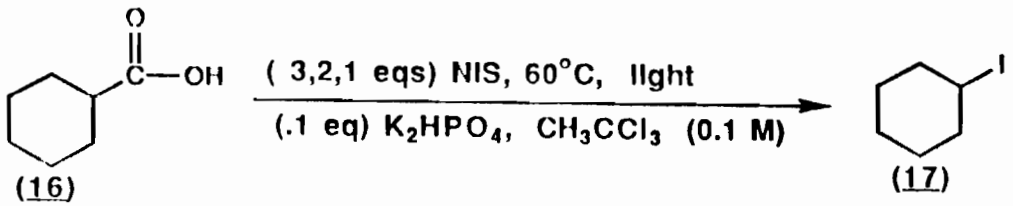
SCHEME 3



Still assuming that the formation of the acyl hypoiodite is a polar reaction, the dipotassium hydrogen phosphate (18), could deprotonate the carboxylic acid (1), pKa=5, thus making the carboxylic acid more nucleophilic by forming its conjugate base (19). Irreversible protonation of the conjugate base of succinimide, pKa=10.5, (21) by potassium dihydrogen phosphate, pKa=7.12, (20) regenerates the catalyst (18) and succinimide (12). Thus dipotassium hydrogen phosphate accomplishes two things, it enhances the nucleophilicity of the reaction and provides another protonation step to drive the equilibrium further to the right. When the reaction (using cyclohexanecarboxylic acid) was run without the dipotassium hydrogen phosphate the maximum yield of cyclohexyl iodide was

80.0% after 6.25 hours, and when the reaction was run with dipotassium hydrogen phosphate the maximum yield of cyclohexyl iodide was 88.8% after 4.5 hours.

This reaction was further optimized by changing the size of the stir bar. The stir bar that had been used was 5/8x3/8 inch, and it was replaced by one that was 7/8x3/8 inch. Since this reaction is heterogeneous the larger stir bar was able to mix the reactants better. After this the reaction was now considered optimized.



(16) (17)

Now that the reaction was considered optimized, other examples of carboxylic acids were used instead of cyclohexanecarboxylic acid. Tertiary and primary (with respect to the alpha carbon) carboxylic acids were also tried in place of cyclohexanecarboxylic acid, a secondary carboxylic acid (see Table 2).

TABLE 2

ARBOXYLIC ACID	GC YIELD %	ISOL. %YIELD	TIME (hrs.)	TEMP (°C)
‘clohexanecarboxylic acid	89	21.6	3.25	60
Undecanoic acid*	52	59.6	6.0	70
‘yl-1cyclohexanecarboxylic acid**	---	0.0	2.0	50
‘lopentylpropionic acid**	---	73.3	6.5	70
‘pentanecarboxylic acid**	---	29.2	3.5	60

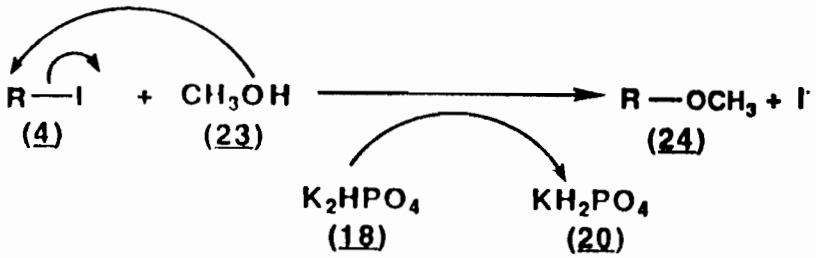
* The yield is higher due to the presence of internal standard in the isolated product

** GC yields of the corresponding alkyl iodide not reported due to the lack of availability of the final product, thus preventing alpha values to be calculated

As is apparent from the data in Table 2, the reaction was only optimized for secondary carboxylic acids. Higher temperatures were required to push the reaction to completion for straight chain carboxylic acids. Apparently tertiary alkyl iodides are incompatible with the reaction conditions. This is not surprising since tertiary alkyl iodides are very likely to undergo S_N1 type reactions, thus the product would decompose to the tertiary carbocation (which may involve itself in numerous other reactions) and the iodide anion.

Also the *in situ* nucleophilic substitution on the incipient alkyl iodide (4) by methanol (23) was examined. The mechanism is thought to proceed as noted in Scheme 4.

SCHEME 4



The alkyl iodide (4) reacts with methanol (23), and a stoichiometric amount of base to form the corresponding methyl ether (24), potassium dihydrogen phosphate (20), and an iodide anion. This reaction is chemoselective because no additional equivalents of NIS are needed, thus the NIS chemoselectively oxidizes the carboxylic acid and does not touch the methanol.

Phenylacetic acid (25) was reacted with NIS, methanol, and dipotassium hydrogen phosphate in 1,1,1-trichloroethane to produce 68.0% of the corresponding methyl ether (26)

$$(C_6H_5)_3CCO_2H \xrightarrow[0.1\ eq\ K_2HPO_4\ \ 50^{\circ}C,\ CH_3CCl_3]{(3,2,1)\ eq.\ NIS\ \ 2\ eq.\ methanol} (C_6H_5)_3COCH_3$$

In conclusion NIS seems to provide a feasible means to oxidatively decarboxylate carboxylic acids to produce the corresponding alkyl iodides and their methyl ethers.

EXPERIMENTAL

INSTRUMENTATION

The reactions were monitored by gas chromatograph analysis on a Hewlett Packard 5700A model equipped with AT-1000 (10% on Chromosorb W AW) filled glass column (8.25 ft long, diameter, 0.25 in.). The AT-1000 was purchased from Applied Science Labs. The carrier gas was nitrogen, bought from liquid carbonic, prepurified, and 99.998% pure. The flow rate of the carrier gas was 30 ml/min.A Hewlett Packard integrator, model number 3396A, was used to integrate the GC spectra. Bromobenzene and o-dichlorobenzene were used as internal standards. Thin layer chromotography was performed using silica gel plates from Analtech and a mixture of 150 toluene:50 ether:15 methanol:1 acetic acid (by volume) was used as the solvent. The product was visualized on the TLC plate using UV light. Infrared spectra were taken with a Mattson Polaris, and NMR spectra were taken with a Varian EM-360L spectrometer. Melting points were determined with a Thomas Hoover Capillary Melting Point Apparatus. All solvents were distilled from calcium hydride under a nitrogen atmosphere and dried 4A° molecular sieves. The carboxylic acids were distilled and all other reagents were used without purification as supplied by Aldrich.

STANDARD SOLUTIONS

Standard solutions were prepared for each reaction mixture

which contained the carboxylic acid, the corresponding alkyl iodide, and an internal standard that separated easily from the other two molecules on the GC. Measured quantities of these compounds were weighed into a 10 ml volumetric flask. The solvent to be used in the reaction was then added to a volume of 10 ml. This solution was then analyzed by gas chromotography three times. The areas of each peak (determined by the integrator) and the amount of each molecule (mmol) were used to determine alpha values for each carboxylic acid and the corresponding alkyl iodide. An alpha value is a ratio of either the carboxylic acid or it's corresponding alkyl iodide to the internal standard. These values are used to determine the amount of carboxylic acid or it's corresponding alkyl iodide in the reaction mixture.

SAMPLE CALCULATION

$$\text{alue of } C_7H_{12}O_2 = \frac{\frac{1.05 \text{ mmol of } C_7H_{12}O_2}{4799661 = \text{peak area of } C_7H_{12}O_2}}{\frac{1.01 \text{ mmol of bromobenzene}}{5083450 = \text{peak area of bromobenzene}}} = 1.10$$

PERCENT YIELD CALCULATIONS

The quantities of molecules in the reaction mixture were calculated by taking a Gas Chromatograph of the reaction mixture and using the peak areas. These areas were then used with the

previously determined alpha value and the amount of the carboxylic acid or it's corresponding alkyl iodide measured into the reaction vessel, to give a percentage of the carboxylic acid or it's corresponding alkyl iodide present in the reaction mixture.

SAMPLE CALCULATION

$$C_7H_{12}O_2 = (1.10)\left(\frac{0.471 \text{ mmol bromobenzene}}{3086013 \text{ area bromobenzene}}\right)(2575693) = 0.440 \text{ mmol}$$

$$C_7H_{12}O_2 = \frac{0.440 \text{ mmol}}{0.811 \text{ mmol}} = 54.2\% \quad C_7H_{12}O_2$$

Where: 1.10= the alpha value of $C_7H_{12}O_2$
0.471 mmol bromobenzene = amount of bromobenzene in the reaction
3086013 = the peak area of bromobenzene
2575693 = the peak area of $C_7H_{12}O_2$
0.811 mmol = mmol of $C_7H_{12}O_2$ that the reaction began with

REACTION CONDITIONS

All reaction solvents were dried over 4A molecular sieves and delivered via 10 ml syringe, the carboxylic acids were distilled, and the NIS was synthesized from N-chlorosuccinimide. All reactions were run under a nitrogen atmosphere and all of the glassware used was oven-dried.

SYNTHESIS OF N-IODOSUCCINIMIDE (NIS)

N-Chlorosuccinimide (NCS, 26.8 g, 0.200 mol) was dissolved in 500 ml of acetone distilled from oven-dried 4A molecular sieves. The distillate was also treated with oven-dried 4A molecular sieves. The reaction was run in an oven-dried, foil wrapped round bottom flask (under a nitrogen atmosphere). In a separate oven-dried foil wrapped flask sodium iodide (30.0 g, 0.200 mol) was dissolved in 500 ml of dry acetone (under a nitrogen atmosphere). When both were completely into solution, the sodium iodide solution was poured into the flask containing the NCS. The resultant mixture was stirred for 30 minutes. At that point, the mixture was vacuum filtered through a sintered glass funnel containing a thin layer of sea sand (all of this glassware was prewashed with dry acetone!). The precipitate was washed with five 100 ml portions of dry acetone to remove any NIS adhering to the sodium iodide precipitate. The filtrate was then concentrated under reduced pressure on the rotary evaporator,making sure the water bath temperature on the rotary evaporaor did not exceed 35°C. When the solvent volume was reduced to approximately 150 ml, the flask was removed from the rotary evaporator and cooled in the freezer for one hour. The resulting crystals were vacuum filtered using a Buchner funnel. The NIS crystals were washed with small portions of ICE COLD dry acetone until they were white. The crystals were transfered into a tared 100 ml 24/40 round bottom flask and the final traces of acetone were removed using the vacuum pump. The yield of NIS was 46.8% with a melting point of 191°C.

OXIDATIVE DECARBOXYLATION OF CYCLOHEXANECARBOXYLIC ACID

USING 1,1,1-TRICHLOROETHANE AS A SOLVENT

Cyclohexanecarboxylic acid (106 mg, 0.827 mmol), and 1,1,1-trichloroethane (8.27 ml, 0.100 M) were added to a 25 ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. Next NIS (558 mg, 2.48 mmol) was introduced into the reaction mixture. An infrared

light was shone directly on the reaction mixture at such a distance to achieve a temperature of 55°C. Alpha values were determined in the standard fashion (cyclohexyl iodide-1.02), using bromobenzene as an internal standard. After reacting for 5 hours, GC analysis indicated that a 59.6% yield of cyclohexyl iodide was produced. After reacting for 6 hours, the yield of the cyclohexyl iodide dropped to 58.3%; therefore, the reaction was terminated.

ANALYZED AT 30 MINUTE INTERVALS

Cyclohexanecarboxylic acid (112 mg, 0.874 mmol), and 1,1,1-trichloroethane (8.74 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. Next NIS (589 mg, 2.62 mmol) was introduced into the reaction mixture. An infrared light was shone directly on the reaction mixture at such a distance to achieve a temperature of 55°C. After reacting for a half hour, the cyclohexyl iodide peak was too small to be integrated by the integrator, thus no yield was recorded. After 3.5 hours GC analysis indicated a 39.2% yield of cyclohexyl iodide. After reacting for 4 hours, GC analysis indicated that a 45.2% of cyclohexyl iodide was produced. At 4.5 hours, GC analysis indicated that the yield of cyclohexyl iodide had dropped to 44.4%; therefore, the reaction was terminated.

REACTING AT 60ºC

Cyclohexanecarboxylic acid (108 mg, 0.843 mmol), and 1,1,1-trichloroethane (8.43 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. Next NIS (569 mg, 2.53 mmol) was introduced into the reaction mixture. An infrared light was shone directly on the reaction mixture at a such a distance to achieve a temperature of 60°C. The temperature was also raised rather quickly, unlike previous reactions, this technique was used on all reactions from this point on. After reacting for 2.5 hours, GC analysis indicated that a 61.6% of cyclohexyl iodide was produced. At 3 hours, GC analysis indicated that the yield of cyclohexyl iodide had dropped to 61.0%; therefore, the reaction was terminated.

REACTING AT 65ºC

Cyclohexanecarboxylic acid (148 mg, 1.15 mmol), and 1,1,1 trichloroethane (11.5 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. Next NIS (779 mg, 3.45 mmol) was introduced into the reaction mixture. An infrared light was shone directly on the reaction mixture at a distance to achieve a temperature of 65°C. After reacting for 2 hours, GC analysis indicated that a 54.4% of cyclohexyl iodide was produced. At

2.5 hours, GC analysis indicated that the yield of cyclohexyl iodide had dropped to 52.9%; therefore, the reaction was terminated.

REACTING AT 45ºC

Cyclohexanecarboxylic acid (109 mg, 0.850 mmol), and 1,1,1-trichloroethane (8.50 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. Next NIS (574 mg, 2.55 mmol) was introduced into the reaction mixture. An infrared light was shone directly on the reaction mixture at such a distance to achieve a temperature of 45°C. After reacting for 4.5 hours, GC analysis indicated that a 17.0% of cyclohexyl iodide was produced. After 4.5 hours the reaction had little solvent left and turned to a yellow solid; therefore, the reaction was terminated.

USING AZOBISISOBUTYRONITRILE AS AN INITIATOR

Cyclohexanecarboxylic acid (109 mg, 0.850 mmol), Azobisisobutyronitrile (2.80 mg, 0.017 mmol), and 1,1,1-trichloroethane (8.50 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. Next NIS (574 mg, 2.55 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. After reacting for 2 hours, GC analysis indicated that a 62.4% of cyclohexyl iodide was produced. At 3 hours, GC analysis indicated that the yield of cyclohexyl iodide had dropped to 62.2%; therefore, the reaction was terminated.

ADDING AN EXTRA EQUIVALENT OF NIS

Cyclohexanecarboxylic acid (120 mg, 0.936 mmol) and 1,1,1-trichloroethane (9.36 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8), reflux condenser, and thermometer. Next NIS (842 mg, 3.74 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. After reacting for 2 hours, GC analysis indicated that a 61.2% of cyclohexyl iodide was produced. At 3 hours, GC analysis indicated that the yield of cyclohexyl iodide had dropped to 57.2%; therefore, the reaction was terminated.

MONITORING REACTION USING 1 H-NMR

Cyclohexanecarboxylic acid (107 mg, 0.835 mmol) and chloroform-d_1 (8.35 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8), reflux condenser, and thermometer. Next NIS (563 mg, 2.51 mmol) was introduced into the reaction mixture. An infrared light was

shone on the reaction mixture at such a distance to achieve a temperature of 60°C. After reacting for 1 hour, 1 H-NMR spectra indicated that no starting material or product was present in the reaction mixture. At 2.5 hours the cyclohexyl iodide was present in the 1 H-NMR spectra, delta 4-4.7 (4H, m), although any starting material was still absent from the spectra. The reaction was terminated.

ADDING TWO EQUIVALENTS OF NIS

Cyclohexanecarboxylic acid (111 mg, 0.866 mmol) and 1,1,1-trichloroethane (8.66 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. Next NIS (.389 mg, 1.73 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. After reacting for 2 hours, GC analysis indicated that a 37.4% of cyclohexyl iodide was produced. At 4 hours, GC analysis indicated that the yield of cyclohexyl iodide was 43.9%; therefore, the reaction was terminated.

ISOLATE PRODUCT (INTERNAL STANDARD NOT ADDED, MONITOR QUALITATIVELY BY GC)

Cyclohexanecarboxylic acid (108 mg, 0.842 mmol) and 1,1,1-trichloroethane (8.42 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. Next NIS (569 mg, 2.53 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at a such a distance to achieve a temperature of 60°C. After reacting for 3 hours, the reaction was considered complete by matching product peaks from this experiment to other product peaks from our most successful reaction thus far. At this point, 5 ml of water and a sufficient amount of sodium thiosulfate, to destroy the triiodide anion and any remaining NIS, was added to the reaction mixture. The mixture was then extracted three times using pentane. The combined organic layers were washed with a saturated solution of sodium chloride. The organic layers from this step were combined and dried over anhydrous sodium sulfate. After the removal of the drying agent, by gravity filtration, the solvent was removed by distillation through a vigreux column at atmospheric pressure under nitrogen. The resultant residue was purified by Kugelrohr distillation at water aspirator pressure. The isolated product (38.2 mg, .189 mmol, 21.6% yield) was a purple oil. The NMR and IR spectra obtained matched the literature spectra for the product.[7]

ADDING 3,2,1 EQUIVALENTS OF NIS TO DRIVE THE REACTION TO COMPLETION

Cyclohexanecarboxylic acid (108 mg, 0..843 mmol) and 1,1,1-

trichloroethane (8.43 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. Next NIS (569 mg, 2.53 mmol) was introduced into the reaction mixture. An infrared light was shone at such a distance to achieve a temperature of 60°C. Although the alpha value for cyclohexanecarboxylic acid was not determined at this time, the cyclohexanecarboxylic acid peak could now be seen and monitored qualitatively because new column packing material (AT-1000) had been obtained. After reacting for 3 hours, (379 mg, 1.69 mmol) of NIS was added to the reaction mixture. After reacting for 5.25 hours, (190 mg, 0.843 mmol) of NIS was added to the reaction mixture. After reacting for 6.25 hours, GC analysis indicated that the cyclohexanecarboxylic acid had been completely consumed, and a yield of 80.0% of cyclohexyl iodide had been produced. The reaction was not worked up.

USING 0.1 EQUIVALENTS OF POTASSIUM DIHYDROGEN PHOSPHATE TO ENHANCE THE NUCLEOPHILICITY OF THE CARBOXYLIC ACID

Cyclohexanecarboxylic acid (110 mg, 0.858 mmol) and 1,1,1-trichloroethane (8.58 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. Next potassium dihydrogen phosphate (K_2HPO_4) (15.0 mg, .0858 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it can deprotonate the carboxylic acid before the NIS is added. At this point, (579 mg, 2.57 mmol) of NIS was added to the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. Alpha values were determined in the standard fashion (cyclohexanecarboxylic acid - 1.12, cyclohexyl iodide - 1.02). After reacting for 2.25 hours, (386 mg, 1.72 mmol) of NIS was added to the reaction mixture. After reacting for 3.75 hours, (193 mg, 0.858 mmol) of NIS was added to the reaction mixture. After reacting for 4.5 hours, GC analysis indicated that the cyclohexanecarboxylic acid had been completely consumed, and an 88.8% yield of cyclohexyl iodide had been produced. The reaction was not worked up.

INTRODUCING 6 EQUIVALENTS OF NIS INTO REACTION MIXTURE ALL AT ONE TIME

Cyclohexanecarboxylic acid (104 mg, 0.811 mmol) and 1,1,1-trichloroethane (8.11 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (14.1 mg, 0.0811 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (1090 mg, 4.87 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of

60°C. After reacting for 3 hours, GC analysis indicated that a 63.9% of cyclohexyl iodide was produced. After reacting for 5 hours, GC analysis still showed that cyclohexanecarboxylic acid was still present in the reaction mixture also there were unknown peaks in the GC spectra, thus the reaction was terminated. The 3,2,1 method for adding NIS seems to give higher yields while using up all of the cyclohexanecarboxylic acid.

INTRODUCING 0.2 EQUIVALENTS OF K_2HPO_4 TO REACTION MIXTURE

Cyclohexanecarboxylic acid (105 mg, 0.819 mmol) and 1,1,1-trichloroethane (8.19 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (28.5 mg, 0.164 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (553 mg, 2.46 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. After reacting for 1.5 hours the reaction was terminated, because GC analysis showed only a 26.5% yield of cyclohexyl iodide. When only 1 equivalent of K_2HPO_4 was used the yield was 78.0% at 1.5 hours, thus obviously more is not always better.

TESTING REPRODUCIBILITY USING THE BEST REACTION CONDITIONS

Cyclohexanecarboxylic acid (107 mg, 0.835 mmol) and 1,1,1-trichloroethane (8.35 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (5/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (14.5 mg, 0.084 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (563 mg, 2.51 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After reacting for 2 hours, (376 mg, 1.67 mmol) of NIS was introduced into the reaction mixture. After reacting for 5.5 hours, (188 mg, 0.835 mmol) of NIS was added to the reaction mixture. After reacting for 6.5 hours, GC analysis indicated that the cyclohexanecarboxylic acid had been completely consumed and a yield of 76.8% of cyclohexyl iodide had been produced. This reaction was not worked up.

USING A LARGER STIR BAR AND CHLOROFORM AS A SOLVENT

Cyclohexanecarboxylic acid (96.4 mg, 0.752 mmol) and chloroform (7.52 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (13.1 mg, 0.075 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (508 mg, 2.26 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After reacting for 0.5 hours, GC analysis indicated that 55.7% cyclohexyl iodide was produced! After reacting for 1.5 hours, (338 mg, 1.50 mmol) of NIS was added to the reaction mixture. After reacting for 2.5 hours, GC analysis indicated that the cyclohexane carboxylic acid had been completely consumed, and the yield of cyclohexyl iodide had dropped from 63.3% (1 hour) to 58.4%. This reaction was not worked up. Since two parameters were changed at once, the cause of the decrease of reaction time is uncertain.

USING A LARGE STIR BAR AND 1,1,1-TRICHLOROETHANE AS THE REACTION SOLVENT

Cyclohexanecarboxylic acid (114 mg, 0.889 mmol) and 1,1,1-trichloroethane (8.89 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (15.4 mg, 0.089 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (600 mg, 2.67 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After reacting for 2 hours, (400 mg, 1.78 mmol) of NIS was added to the reaction mixture. The reaction was terminated because the stir bar stopped spinning in the unattended reaction mixture and the reaction was ruined. Although the reaction was ruined, information was obtained from it. After 0.5 hours, GC analysis indicated that only 19.0% cyclohexyl iodide was produced, and in the reaction ran with chloroform as a solvent, 55.7% cyclohexyl iodide was produced according to GC analysis.

USING CHLOROFORM AS THE REACTION SOLVENT

Cyclohexanecarboxylic acid (106 mg, 0.827 mmol) and chloroform (8.27 ml, 0.100 M) were added to a 25ml 14/20 two

necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (14.4 mg, 0.083 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (558 mg, 2.48 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After reacting for 1.3 hours, (372 mg, 1.65 mmol) of NIS was added to the reaction mixture. After reacting for 3 hours, GC analysis indicated that 70.7% cyclohexyl iodide had been produced, but the reaction was terminated because of foreign peaks in the Gas Chromatography.

USING A TUNGSTEN LAMP AS THE LIGHT SOURCE

Cyclohexanecarboxylic acid (107 mg, 0.835 mmol) and 1,1,1-trichloroethane (8.35 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (14.7 mg, 0.084 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (564 mg, 2.51 mmol) was introduced into the reaction mixture. A tungsten light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After reacting for 3.5 hours, (376 mg, 1.67 mmol) of NIS was added to the reaction mixture. After reacting for 4.5 hours, GC analysis indicated that the cyclohexanecarboxylic acid had been consumed, and a yield of 62.9% cyclohexyl iodide had been produced. The reaction was not worked up.

USING CESIUM CARBONATE TO DEPROTONATE THE CYCLOHEXANECARBOXYLIC ACID COMPLETELY

Cyclohexanecarboxylic acid (99.3 mg, 0.775 mmol) and 1,1,1-trichloroethane (7.75 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next Cs_2CO_3 (253 mg, 0.775 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (523 mg, 2.33 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of

60°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After reacting for 1 hour the reaction turned yellow (usually is purple) and GC analysis showed many uninterpretable peaks, thus the reaction was discarded.

REPLACING NIS WITH N-BROMOSUCCINIMIDE (NBS) TO OBTAIN THE CORRESPONDING ALKYL BROMIDE

Cyclohexanecarboxylic acid (102 mg, 0.796 mmol) and 1,1,1-trichloroethane (7.96 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (13.9 mg, 0.080 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (425 mg, 2.39 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After reacting for 2.5 hours, GC analysis indicated that cyclohexyl bromide had not been produced. The temperature of the reaction mixture was raised until the reaction mixture was refluxing. After reacting for 3.5 hours, GC analysis indicated that there still was not any cyclohexyl bromide produced, thus the reaction was discarded.

REPLACING NIS WITH N-CHLOROSUCCINIMIDE (NCS) TO OBTAIN THE CORRESPONDING ALKYL CHLORIDE

Cyclohexanecarboxylic acid (108 mg, 0.843 mmol) and 1,1,1-trichloroethane (7.75 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (14.7 mg, 0.084 mmol) was introduced into the reaction mixture and allowed to stir for about 5 minutes, so it could deprotonate the carboxylic acid before the NIS was added. Next NCS (338 mg, 2.53 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to reflux the reaction mixture. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After reacting for 3 hours, GC analysis indicated that cyclohexyl chloride had not formed, thus the reaction was discarded.

OXIDATIVE DECARBOXYLATION OF UNDECANOIC ACID

REACTING AT 60°C

Undecanoic acid (98.0 mg, 0.526 mmol) and 1,1,1-

trichloroethane (5.26 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (9.16 mg, 0.053 mmol) was introduced into the reaction, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (355 mg, 1.58 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. Alpha values were determined in the standard fashion (undecanoic acid-.638 1-iododecane-.667). After reacting for 2.5 hours, GC analysis indicated that only a 17.7% yield of 1-iododecane had been produced. The reaction was then discarded.

REACTING AT 70°C

Undecanoic acid (121 mg, 0.649 mmol) and 1,1,1-trichloroethane (6.49 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (11.3 mg, 0.065 mmol) was introduced into the reaction, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (438 mg, 1.95 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 70°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After 1.5 hours, NIS (292 mg, 1.30 mmol) was added to the reaction mixture. After 3.5 hours, NIS (146 mg, 0.649 mmol) was added to the reaction mixture. After reacting for 4.5 hours, GC analysis indicated that a 64.1% yield of 1-iododecane had been produced and the undecanoic acid had been consumed. The reaction was not worked up.

REACTING AT 70°C

Undecanoic acid (149 mg, 0.800 mmol) and 1,1,1-trichloroethane (8.00 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (13.9 mg, 0.080 mmol) was introduced into the reaction, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (540 mg, 2.40 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 70°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After 2 hours, NIS (360 mg, 1.60 mmol) was added to the reaction mixture. After 3 hours, NIS (180 mg, 0.800 mmol) was added to the reaction

mixture. After reacting for 6 hours, GC analysis indicated that the undecanoic acid had been consumed, and a 52.6% yield of 1-iododecane had been produced. At this point the reaction was worked up in the standard fashion. The resultant residue was purified by Kugelrohr distillation at water aspirator pressure. The product, a dark purple oil, yielded 160 mg (0.597 mmol, 59.6%). The reason the yield was higher than the GC yield was due to the amount of internal standard that was also isolated in the product. IR ($CDCL_3$) 2950, 2890, 2400, 2299, 1475, 920 cm^{-1}. 1 H-NMR delta 0.66-1.0 (2 H, q), 1.23 (17 H, s), 3.0-3.43 (3 H, t).

OXIDATIVE DECARBOXYLATION OF 1-METHYL-1-CYCLOHEXANECARBOXYLIC ACID

REACTING AT 60ºC

1-methyl-1-cyclohexanecarboxylic acid (136 mg, 0.956 mmol) and 1,1,1-trichloroethane (9.56 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (16.7 mg, 0.096 mmol) was introduced into the reaction, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (645 mg, 2.88 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. The reaction was monitored qualitatively using gas chromatography. After reacting for 2 hours, no product had been produced thus the reaction was discarded.

REACTING AT 50ºC

1-methyl-1-cyclohexanecarboxylic acid (143 mg, 1.01 mmol) and 1,1,1-trichloroethane (10.1 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (17.5 mg, 0.101 mmol) was introduced into the reaction, so it could deprotonate the carboxylic acid before the NIS was added. Next NIS (682 mg, 3.03 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 50°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. The reaction was monitored qualitatively using gas chromatography. After reacting for 3 hours, no product had been produced thus the reaction was discarded.

ADDING NO K_2HPO_4

1-methyl-1-cyclohexanecarboxylic acid (133 mg, 0.935 mmol) and 1,1,1-trichloroethane (9.35 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next NIS (631 mg, 2.81 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 50°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. The reaction was monitored qualitatively using gas chromatography. After reacting for 3 hours, no product had been produced thus the reaction was discarded.

OXIDATIVE DECARBOXYLATION OF 3-CYCLOPENTYLPROPIONIC ACID

3-Cyclopentylpropionic acid (138 mg, 0.970 mmol) and 1,1,1-trichloroethane (9.70 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (16.9 mg, 0.097 mmol) was introduced into the reaction mixture and allowed to stir for 5 minutes in order to deprotonate the carboxylic acid before adding the NIS. Next NIS (655 mg, 2.91 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 70°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. The reaction was monitored qualitatively using gas chromatography. After reacting for 2 hours, NIS (436 mg, 1.94 mmol) was added to the reaction mixture. After reacting for 3.5 hours, NIS (218 mg, 0.970 mmol) was added to the reaction mixture. After 6 hours, GC analysis indicated that the 3-cyclopentylpropionic acid was almost completely consumed. thus the reaction was considered complete. At this point, the reaction was worked up in the standard fashion. The resultant residue was purified by Kugelrohr distillation at water aspirator pressure. The product yielded 159 mg (0.711 mmol, 73.3%) of purple oil. IR ($CDCL_3$) 3450, 3000, 2900, 1725, 925, 750 cm^{-1}. 1 H-NMR delta 2.93-3.33 (2 H, t), 0.66-2.1 (11 H, m).

OXIDATIVE DECARBOXYLATION OF CYCLOPENTANECARBOXYLIC ACID

Cyclopentanecarboxylic acid (103 mg, 0.902 mmol) and 1,1,1-trichloroethane (9.02 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (15.7 mg, 0.090 mmol) was introduced into the reaction mixture and allowed to stir for 5 minutes, in

order to deprotonate the carboxylic acid. Next NIS (609 mg, 2.71 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 60°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. The reaction was monitored qualitatively using gas chromatography. After reacting for 1.5 hours, NIS (406 mg, 1.80 mmol) was added to the reaction mixture. After reacting for 2.75 hours, NIS (203 mg, 0.902 mmol) was added to the reaction mixture. After reacting for 3.5 hours GC analysis indicated that the carboxylic acid had been almost completely consumed. The reaction was then worked up in the standard fashion. The resultant residue was purified by Kugelrohr distillation at water aspirator pressure. The product yielded 51.5 mg (0.263 mmol, 29.2%) as a purple oil. The isolated yield is so low is because of the volatility of the product. IR ($CDCL_3$) 3450, 2975, 1710, 910, 750 cm^{-1}. 1 H-NMR delta 4.07-4.57 (1 H, m), 1.33-2.66 (8 H, m).

IN SITU NUCLEOPHILIC SUBSTITUTION OF THE INCIPIENT ALKYL IODIDE BY METHANOL

OXIDATION DECARBOXYLATION OF 1-METHYL-1-CYCLOHEXANECARBOXYLIC ACID

1-Methyl-1-cyclohexanecarboxylic acid (116 mg, 0.816 mmol), methanol (66.0 ul, 1.63 mmol), and 1,1,1 trichloroethane (8.16 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent solvent loss during the reaction. Next K_2HPO_4 (156 mg, 0.898 mmol) was introduced into the reaction mixture and allowed to stir for 5 minutes, in order to deprotonate the carboxylic acid. Next NIS (551 mg, 2.45 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 50°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. The reaction was monitored qualitatively using gas chromatography. After reacting for 2.5 hours, GC analysis showed many uninterpretable peaks thus the reaction was discarded.

OXIDATIVE DECARBOXYLATION OF TRIPHENYLACETIC ACID

Triphenylacetic acid (183 mg, 0.635 mmol), methanol (51.0 ul, 1.27 mmol), and 1,1,1 trichloroethane (6.35 ml, 0.100 M) were added to a 25ml 14/20 two necked round bottom flask equipped with a stir bar (7/8 inch), reflux condenser, and thermometer. An ice water circulator was used to cool the condenser column to prevent

solvent loss during the reaction. Next K_2HPO_4 (122 mg, 0.699 mmol) was introduced into the reaction mixture and allowed to stir for 5 minutes, in order to deprotonate the carboxylic acid. Next NIS (714 mg, 3.18 mmol) was introduced into the reaction mixture. An infrared light was shone on the reaction mixture at such a distance to achieve a temperature of 50°C. A funnel wrapped with tin foil was used to maximize the amount of light on the reaction vessel. After reacting for 3 hours, NIS (143 mg, 0.635 mmol) was added to the reaction mixture. Thin layer chromotography was used to moniter this reaction. After 5 hours, TLC (150 toluene:50 ether:15 methanol:1 acetic acid, and glass was used to illuminate the reaction on the TLC plate) indicated that the reaction was complete. At this point the reaction mixture was worked up in the standard fashion. After extraction of the product, the solution was rotovapped to eliminate the solvent. Column chromotography was set up using a 2% ether/hexane solution as the mobile phase to further purify the product. The product was collected in fractions #3-8. These fractions were combined and quantitatively transferred to one round bottom flask. The solution was rotovapped. The product, a colorless oil, yielded 118 mg (0.431 mmol, 68.0%). IR ($CDCL_3$) 3100, 2950, 2850, 2299, 1610, 1500, 1460, 1100 cm^{-1}. 1 H-NMR delta 6.83-7.66 (15 H, s), 2.66-3.0 (3 H, s).

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