Optimization of Reaction Variables in the Selective Hydrodechlorination of Chlorinated Phthalic Anhydrides and Acids: Preparation of 3,6-Dichlorophthalic Acid and 3-Chlorophthalic Acid[1]

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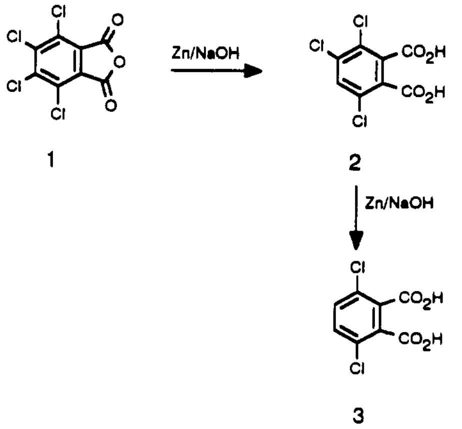
Received August 7, 1992

Chlorinated phthalic acids are useful intermediates in the synthesis of a number of valuable compounds.[2] While these deceivingly simple looking materials have been prepared by chlorination of phthalic anhydride, either in the liquid[3] or vapor phase,[4] these methods suffer from the lack of selectivity of addition of chlorine (be it one, two, or more) and a tedious separation procedure to obtain a pure product. A second strategy toward monochlorophthalic anhydrides involves nitration of phthalic anhydride[5] or its phthalimide derivative,[6] followed by chlorodenitration of the resultant nitrophthalic acid or nitrophthalimide. The former procedure suffers from the poor selectivity for nitration (approximately a 60:40 ratio of 4- to 3-nitrophthalic anhydride), while the latter suffers from a protection/deprotection scheme.

We have previously reported an alternate methodology toward the synthesis of polychlorophthalic acids. Treatment of tetrachlorophthalic anhydride, **1**, with zinc and aqueous sodium hydroxide led to nearly exclusive formation of 3,4,6-trichlorophthalic acid, **2**.[7] Hydrodechlorination of **1** proceeded in high yield and with remarkable selectivity. The structure of **2** was proven by further hydrodechlorination to the known 3,6-dichlorophthalic acid **3** via removal of a second chlorine (Scheme I). The selectivity observed in both reactions has prompted further exploration of this methodology.

Initial experiments were designed to study and optimize the reaction variables for preparation of **2** from **1**. We knew from our exploratory experiments excellent yields and selectivities for **2** could be obtained (85–95% isolated yield, 98% purity).[7] In a series of reactions, the temperature (65 or 105 °C), amount of zinc (1.5 or 3.0 equiv), concentration (5% or 20%), and amount of sodium hydroxide (5 or 10 mL) were adjusted in a systematic manner. Reactions were monitored by GC and the yields were determined based upon maximum area percentage for formation of **2**. Control experiments showed that the area percentage on the GC traces matched closely with the isolated yields of **2** in these series of experiments and each of the desired products in subsequent experiments. Control of reaction times in all of the experiments was crucial in that if the reaction ran too long overreduced products tended to appear in significant amounts, while reactions stopped prematurely led to incomplete conversion to the desired products.

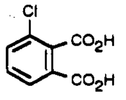
Scheme I. Hydrodechlorination of 1



A simple way of displaying the results of these experiments is in terms of a two-factorial diagram, which clearly shows the symmetrical nature of the experimental design and the relationships between various data points (Figure 1). In this diagram, each point at the corner of the cube represents the maximum yield of **2** (GC area %) resulting from that particular set of conditions, somewhat like a four-dimensional graph. In Figure 1, all experiments were run on a 1.0-g scale and with either 1.5 or 3 equiv of zinc.

Inspection of these results reveal the dramatic differences in yield of **2** obtained by systematic adjustments in the reaction variables. The highest yield (96.7%) was obtained using 3 equiv of zinc with 10% NaOH at 65 °C. A more practical set of conditions would be to use less zinc (1.5 equiv), since only a minor decrease in yield was observed. Comparison of the optimum yielding conditions found in the experimental design with those originally reported[7] indicated that the initial reaction conditions chosen were fortuitously close to the optimum conditions in the design.

A second set of similar experiments was run on the hydrodechlorination of **1** wherein the goal was to maximize the yield of **3**. Our exploratory reactions had shown that harsher reaction conditions were necessary to effect the removal of a second chlorine. Therefore, in general, longer reaction times were used. Figure 2 reveals that the best yield of **3** (75.8%) was obtained using 10% NaOH with 3 equiv of zinc at 105 °C. At higher sodium hydroxide concentrations (20%), significant amounts of 3-chlorophthalic acid, **4**, were formed from overreduction of **3**.



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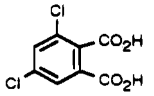

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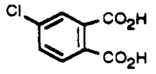

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The results in Figure 2 showed again that systematic changes in the reaction variables led to very large differences in the amount of **3** that was formed. Although

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[1] Portions of this work were previously presented at the 201st Meeting of the American Chemcial Society, Atlanta, GA, April 14-19, 1991, ORGN 237.

[2] Use as plant growth regulators: Diehl, R. E.; Walworth, B. L. U.S. Patent 4,017,299, 1977; *Chem. Abstr.* **1977,** *87,* 52974e. For the use of **2** as a starting material for 2,4,5-trifluorobenzoic acid, a valuable quinolone intermediate, see: O'Reilly, N. J.; Derwin, W. S.; Fertel, L. B.; Lin, H. C. *Synlett* **1990,** 609.

[3] Villager, V. *Chem. Ber.* **1909,** *42,* 3529. Zweig, A.; Epstein, M. *J. Org. Chem.* **1978,** *43,* 3690.

[4] Verbicky, J. W.; Williams, L. *J. Org. Chem.* **1983,** *48,* 2465.

[5] Lawrence, W. A. *J. Am. Chem. Soc.* **1920,** *42,* 1871. Culhane, P. J.; Woodward, G. E. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 408.

[6] Nitration of N-alkyl phthalimides: Williams, F. J.; Donahue, P. E. *J. Org. Chem.* **1978,** *43,* 1608.

[7] For an experimental procedure detailing the preparation of **2** from **1** see: O'Reilly, N. J.; Derwin, W. S.; Lin, H. C. *Synlett* **1990,** 339.

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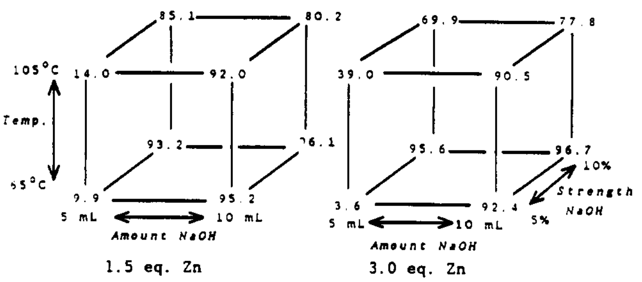

1.5 eq. Zn 3.0 eq. Zn

Figure 1. Maximum yields of 2 from 1.

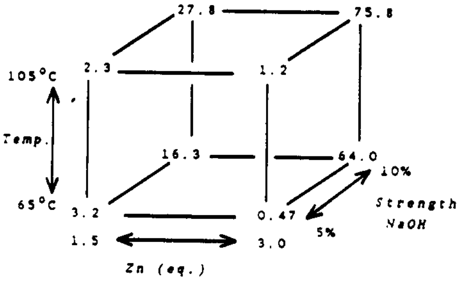

Figure 2. Maximum yields of 3 from 1.

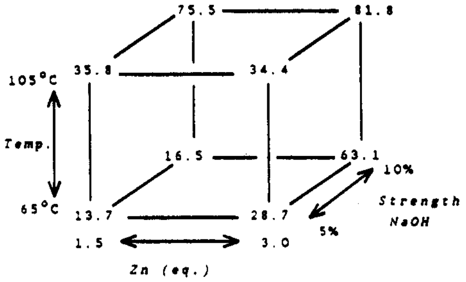

Figure 3. Maximum yields of 3 from 2.

the selectivity was not as high as in the previous set of experiments for formation of 2, the reaction represents a second example of very good hydrodechlorination selectivity. One minor byproduct observed in the reaction was 3,5-dichlorophthalic acid 5, formed in up to 10% yield under certain reaction conditions. Experiments were run in an attempt to improve the yield of 5, but they were unsuccessful.[8]

Thus, good selectivity could be obtained in the removal of either one or two chlorines from 1. With the above results in hand, it was necessary to run a similar series of experiments on the hydrodechlorination of 2 to 3, as well as hydrodechlorination of 2 to 4. The questions that we desired an answer to were as follows: (a) could the selectivity of hydrodechlorination of 2 to 3 be improved relative to that of 1 to 3, and (b) what was the selectivity of hydrodechlorination of 4 from 2?

The results for the hydrodechlorination of 2 to 3 are summarized in Figure 3. Results from the experimental design indicated that the maximum yield of 3 via hydrodechlorination of 2 was slightly higher (81.8%) than could be obtained from 1. As with 1, the use of 20% NaOH led to formation of large amounts of 4, thus lowering the selectivity of the reaction. Approximately the same amount of 5 was formed in the reaction as in previous experiments (10%).

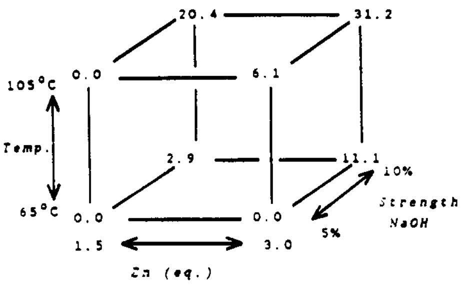

Figure 4. Maximum yields of 4 from 2.

On the basis of these results, a preparative reaction of 3 from 2 was run (5.7 equiv of zinc dust, 10% NaOH at 100 °C for 3.5 h), from which a 72% isolated yield of 3 (96% pure) was obtained.

The reaction variables for the optimized preparation of 4 from 2 were also studied; the results are displayed in Figure 4. The overall selectivity in the formation of 4 was not nearly as high as in the previous cases. The reaction mixture was contaminated with significant amounts of 3, 5, 4-chlorophthalic anhydride (6), and phthalic anhydride. As noted above, the general empirical trend noticed in these experiments was that as each chlorine is removed, the remaining chlorines become harder to remove, and thus harsher conditions (leading to lower selectivities) need to be utilized.

On the basis of the results obtained in the experimental design for the preparation of 4, it was necessary to go outside the variable limits of the cube to obtain useful selectivities. To this end, the use of 5.7 equiv of zinc and 20% NaOH at 118 °C for long reaction periods led to a 57% isolated yield of 4 at an 85% purity. Recrystallization from water led to material of >99% purity.

In conclusion, statistical design studies of the reaction variables for hydrodechlorination of 1 and 2 indicated that good selectivities for formation of 2, 3, and 4 could be obtained. Optimization of reaction variables based upon the results of the statistical design experiments led to developing conditions for preparatively useful procedures to each of 2, 3, and 4. Selectivity for removal of the chlorine is truly remarkable in each case. This methodology represents a unique, flexible, and very simple entryway to these types of chlorinated phthalic acids, materials which are difficult, if not impossible, to obtain by other means.

Experimental Section

General Procedure for Hydrodechlorination Experimental Design. In a small round-bottom flask was placed 1.0 g of 1 or 2, along with the appropriate amount of aqueous NaOH and zinc dust (zinc 64, New Jersey Zinc Co.). The reaction was heated to the desired temperature, and aliquots were taken periodically, quenched with aqueous HCl, and extracted into EtOAc. Assays of the aliquots were performed via capillary GC (30-m DB-5 column on an HP 5890 GC using an FID detector). Products were identified by comparison to known compounds.

Preparation of 3,6-Dichlorophthalic Acid (3) from 2. Charged together were 10.0 g (0.037 mol) of 2, 14 g (0.21 mol) of zinc dust, and 100 mL of 10% aqueous NaOH. The reactants were stirred vigorously and heated to 100 °C for 3.5 h. After the mixture was allowed to cool to room temperature, the zinc salts were filtered off and washed with H_2O (3 × 25 mL). Acidification of the filtrate with concd HCl to a pH of 2 led to small amounts of a solid material which was filtered off and dried. This material (2.45 g) was identified as the monosodium salt of a mixture of

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[8] Recent results have shown that hydrodechlorination of tetrachloro-N-alkylphthalimides using similar conditions as stated in this paper lead to 5 as the major product (U.S. Patent 5,086,188, 1992). A manuscript describing this conversion as well as a mechanistic speculation as to the differences noted in the hydrodechlorination selectivities is in preparation.

chlorinated phthalic acids, with the purity being very low. The remaining filtrate was further acidified to a pH of 0.5 by slow continual addition of concd HCl, with good stirring. The product was extracted with EtOAc (4 × 100 mL), and the combined organic layers were dried over $MgSO_4$. The solution was filtered, the solvent was removed on a rotary evaporator, and the resultant solids were dried in a vacuum desiccator (60 °C, 10 mmHg) to give **3** (5.85 g, 72.2% yield, 96% purity by GC), analysis as the anhydride mp 190.5–192 °C (lit.[9] mp 194.5 °C). The retention time and ^{13}C NMR spectrum of this material was identical to that of an authentic sample.

Preparation of 3-Chlorophthalic Acid (4) from 2. Charged together were 10.0 g (0.037 mol) of **2**, 14 g (0.21 mol) of zinc dust, and 100 mL of 20% aqueous NaOH. The reaction was stirred and heated at 115 °C for 65 h. Workup as described above led to **4** (3.95 g, 57% yield, 84.9% purity by GC). A 3.0-g sample was recrystallized from water to yield 2.16 g of **4** of 99% purity by GC, mp 184–185 °C (lit.[10] mp 186 °C). The ^{13}C NMR spectrum and the retention time of this material was identical to that of an authentic sample.

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(10) Neumann, R.; Scheuer, P. G. *J. Am. Chem. Soc.* **1956**, *78*, 5004.