Organic Process Research & Development **1998**, *2,* 111–115

Process Improvements in the Synthesis of 2,4,5-Trifluorobenzoic Acid. Selective Hydrodefluorination of Tetrafluorophthalimides

Lawrence B. Fertel*

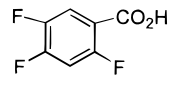
Occidental Chemical Corporation, Technology Center, 2801 Long Road, Grand Island, New York 14072

Abstract:

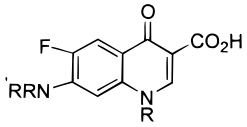
An improved preparation of the fluoroquinolone antibacterial intermediate 2,4,5-trifluorobenzoic acid is described. A combination of a selective hydrodefluorination and hydrolysis reaction of 3,4,5,6-tetrafluoro-*N*-methylphthalimide leading to 3,5,6-trifluorophthalic acid was key to the success of the process. In addition the development of a two-step, one-pot imidization/halogen exchange from tetrachlorophthalic anhydride to 3,4,5,6-tetrafluoro-*N*-methylphthalimide in sulfolane solvent is detailed.

Introduction

We have previously reported on our efforts towards the synthesis of 2,4,5-trifluorobenzoic acid (**1**).[1] This compound has been shown to be valuable in the synthesis of a number of fluoroquinolone antibacterials,[2] the general structure of which is shown below. The quinolones are a relatively new class of anti-infective agents which have been shown to be effective against a number of bacteria strains. They are useful in the treatment of urinary tract infections, as well as eye, ear, nose, and throat infections. The quinolones constitute the fastest growing segment of the multi billion dollar anti-infective market.[3]

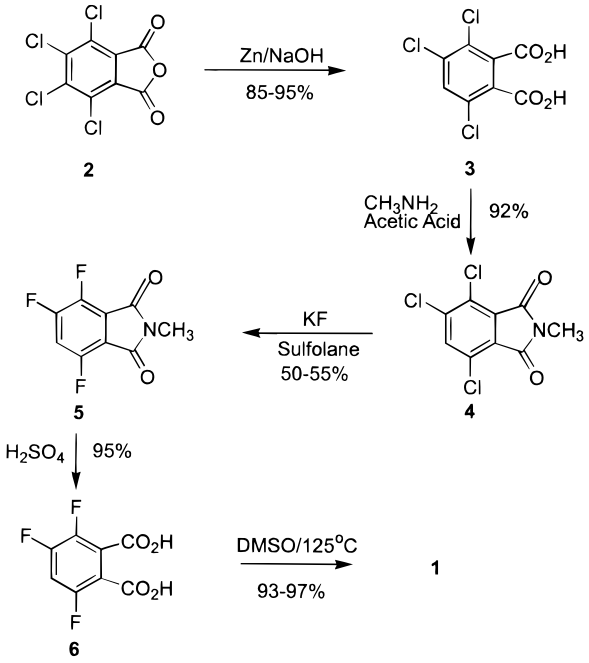


1



One of the key reaction steps in our original synthesis of **1** was a selective hydrodechlorination of commercially available tetrachlorophthalic anhydride (**2**) to 3,4,6-trichlorophthalic acid (**3**) by treatment with zinc in an aqueous caustic solution[4] (Scheme 1). Following protection of the diacid as the *N*-methyltrichlorophthalimide **4** using anhydrous methylamine in glacial acetic acid and halogen exchange with spray-dried potassium fluoride in sulfolane, the resultant trifluorophthalimide **5** was hydrolyzed to 3,4,6-trifluorophthalic acid (**6**). Heating **6** with any one of several dipolar aprotic solvents such as dimethyl sulfoxide (DMSO) or

Scheme 1. **Original route to 1**



N-methyl-2-pyrrolidinone (NMP) led to a selective decarboxylation, giving trifluorobenzoic acid **1**.[5]

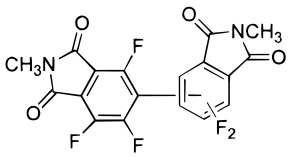
Despite the excellent yields for the hydrodechlorination, imidization/hydrolysis, and decarboxylation steps, the overall yield of the synthesis suffered due to low yields obtained in the halogen-exchange reaction of trichlorophthalimide **4**. On scale-up, at best 50−55% isolated yields for the conversion of **4** to **5** were obtained.

Analysis of the residue from the reaction indicated that the low yields seen in the reaction were primarily due to decomposition of the product under the reaction conditions. Upon formation of trifluorophthalimide **5**, it apparently underwent a competing self-coupling reaction leading to polyfluorinated biphenyl phthalimides of the general structure shown below.[6] Thus, the low yields were a function of the instability of **5** to the reaction conditions. We rationalized the formation of the biphenyls as coming about from proton abstraction from one molecule of **5** by the excess KF present.[7] The resulting aryl anion could then displace a fluoride on a second molecule of **5**, leading to the observed biphenyl species.

* E-mail: Larry_Fertel@oxy.com. Fax: 716 773 8110.

(1) O'Reilly, N. J.; Derwin, W. S.; Fertel, L. B.; Lin, H. C. *Synlett* **1990**, 609.
(2) Bouzard, D. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukas, G, Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; p 257.
(3) Chu, D. T. W.; Mitschner, L. A.; Zavod, R. M.; Devasthale, P. V.; Shen, L. L.; Sharma, P. N.; Pernet, A. G. *Chemtech* **1991**, 50. Grohe, K. *Chem. Br.* **1992**, 34.
(4) O'Reilly, N. J.; Derwin, W. S.; Lin, H. C. *Synlett* **1990**, 339. O'Reilly, N. J.; Dewin, W. S.; Lin, H. C. US 4981999, 1991.
(5) O'Reilly, N. J.; Derwin, W. S.; Lin, H. C. US 5233085, 1992.
(6) L. B. Fertel, unpublished results.
(7) KF is well-known to act as a base in dipolar, aprotic slovents such as sulfolane: Clark, J. H. *Chem. Rev.* **1980**, 429.

S1083-6160(97)00244-2 CCC: $15.00
Published on Web 02/14/1998

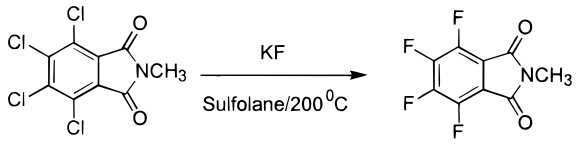


The overall yield of the route from **2** to **1** was thus limited to about 35% over five steps, making this an economically unfeasible process. It was thus incumbent upon us to find a way around the problem of the troublesome halogen-exchange reaction of **4** in order to increase the total overall yield.

In addition, the original process for the conversion of **3** to **4** used glacial acetic acid as the solvent. While the yield in the reaction was excellent, it took repeated water washings to completely remove all traces of acetic acid from **4**, which then had to be isolated in an anhydrous condition prior to the halogen-exchange reaction. Reduction of the cost of the overall process required elimination of glacial acetic acid, simplification of the isolation of **4**, and minimization of the aqueous waste.

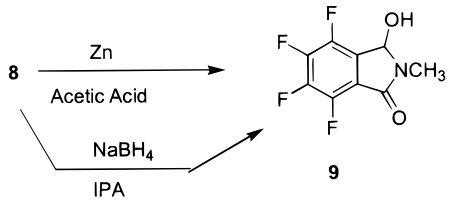
Results and Discussion

Hydrodefluorination. It was known that, in contrast to the problems seen in the halogen-exchange reaction of **4**, conversion of tetrachlorophthalimide **7** to tetrafluorophthalimide **8** using similar conditions (KF, sulfolane, 200 °C) as shown below proceeded in greater than 85% yields.[8] On the basis of the reasoning behind the poor fluorination yields in the conversion of **4** to **5**, we presumed that, once tetrafluorophthalimide was formed, the lack of an aromatic hydrogen in **8** would lead to an increase in its isolated yield due to the elimination of the competing reaction which could form biphenyls. We then realized that if a fluorine could be selectively removed from tetrafluorophthalimide **8**, this could lead directly to trifluorophthalimide **5**, which could then be taken on to trifluorobenzoic acid **1** as originally designed. Since the remaining steps were all high yielding, the bottleneck for increased yields could be overcome.

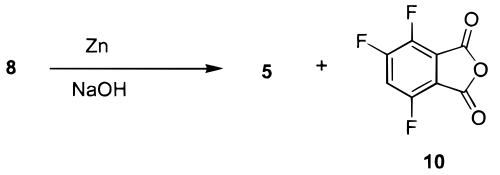


7 **8**

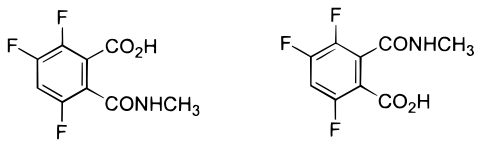
Hydrodefluorination of aromatic fluorine derivatives is a known reaction. Typical conditions are zinc, in either sulfuric acid[9] or acetic acid[10] (used for tetrafluorophthalonitriles), or other reductive methods such as sodium borohydride[11] or palladium on carbon.[12] Initial attempts to effect hydrodefluorination of **8** using the above conditions were not successful. Treatment of **8** with zinc in either acetic acid or sulfuric acid did not lead to removal of a fluorine. Instead, reduction of one of the phthalimide carbonyl groups occurred, leading to **9** as the sole product. The same product was also formed upon treatment of **8** with sodium borohydride in isopropyl alcohol.



However, addition of **8** to an aqueous solution of sodium hydroxide in the presence of zinc dust at 60 °C led to the formation of two species, which, by interpretation of the mass spectra, indicated that the molecular weights of the major products were consistent with **5** and 3,4,6-trifluorophthalic anhydride (**10**).[13] Despite this apparent success with removal of a fluorine, at this point we did not know which fluorine was removed. However, on the basis of our experience in hydrodechlorination chemistry, we believed that we had indeed been successful.



Isolation of the solids from the reaction and analysis by ^{19}F NMR led to two important pieces of information. The first was that trifluorophthalimide **5** and **10** were not being formed. Instead, the products resulting from addition of water to the phthalimide ring had been formed, namely, trifluorophthalamic acid **11** or **12** and phthalic acid **6**. This discrepancy in the analysis occurred because we were detecting the closed forms of both the phthalamic acid and the phthalic acid by GC/MS; they both cyclized by dehydration upon injection onto the GC injection port.



11 **12**

The second piece of information from the NMR data was that the correct fluorine had been removed. This was proven by completely hydrolyzing the reaction products by heating at 160 °C in 60% aqueous sulfuric acid. This led to exclusive

(8) Itoh, H.; Matsushita, U.; Shimizu, T.; Ishikawa, N.; Shimizu, M. US Patent 4,769,493, 1988; *Chem. Abstr.* **1988**, *109*, 128588j. L. Fertel, Unpublished results.

(9) Yoshida, M.; Sasaki, M.; Niizeki, S. Jpn. Kokai Tokkyo Koho JP 01/258639, 1990; *Chem. Abstr.* **1990**, *112*, 178350h. Niizeki, S.; Sasaki, M.; Yoshida, M.; Soejima, K. Jpn. Kokai Tokkyo Koho JP 01/160944, 1990; *Chem. Abstr.* **1990**, *112*, 55243t.

(10) Yoshida, M.; Sasaki, M.; Niizeki, S. Jpn. Kokai Tokkyo Koho JP 02/169542, 1990; *Chem. Abstr.* **1991**, *113*, 190932c. Yoshida, M.; Sasaki, M.; Niizeki, S. Jpn. Kokai Tokkyo Koho JP 02/117643, 1990; *Chem. Abstr.* **1991**, *113*, 131769g.

(11) Kobayashi, H.; Shimizu, M. EP 307897, 1989; *Chem. Abstr.* **1989**, *111*, 133801u.

(12) Naumann, K.; Branden, R. DE 3,705,410, 1988; *Chem. Abstr.* **1988**, *110*, 23543h.

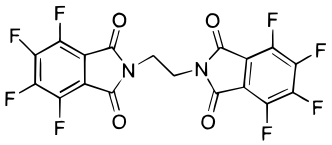
(13) Stults, J.; Fertel, L. B.; Derwin, W. S. U.S. Patent 5,294,738, 1994.

formation of **6**, which was subsequently compared with authentic material previously synthesized by our original route. Additionally, a successful synthesis of trifluorobenzoic acid **1** was accomplished with the desired isomer specificity using the material formed from the new route.

In order to determine the structure of the phthalamic acid as being that of either **11** or **12**, attempts were made to synthesize authentic samples of both. We hoped to open up the phthalimide ring to produce both isomers by treatment of trifluorophthalimide **5** with potassium bicarbonate,[14] as well as heating **5** with a water/THF mixture. Both attempts, however, were unsuccessful. The fact that we were unable to determine the structure as being **11** or **12** was not of consequence as either one can be taken onto **1**.

Typical isolated yields for the hydrodefluorination reaction were excellent, ranging around 90%. Optimization of the reaction conditions for the hydrodefluorination reaction indicated that the best results were obtained by using just over 2 equiv of NaOH and 3 equiv of zinc dust at a temperature around 60 °C. We noticed an exotherm upon addition of the zinc dust; therefore, on a large scale, the zinc is best added portionwise over a period of 0.5 h. Assays of the solid taken at the end of the reaction indicated that 78% of **11** or **12** and 15% of **6** were being formed. This mixture was formed in essentially the same ratio under various reaction conditions. Increases in reaction times, as well as the addition of extra sodium hydroxide, did not increase the conversion of **11** or **12** to **6**. We do not have an explanation for the lack of further conversion to **6** past the typical 15% seen at the end of the reaction.

The reaction appears to be general for other substituted phthalimides, such as the N-phenyl and *N*-ethyl derivatives. In addition, exposure of *N*,*N*′-dimethylenebis(tetrafluorophthalimide) (**13**) to the reaction conditions led to a 55% isolated yield of **6**.



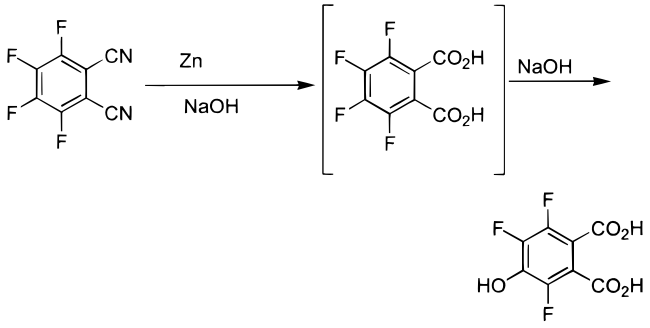
13

For larger scale reactions, the intermediates were not isolated after the defluorination reaction. The filtrate, after removal of the zinc salts via filtration, was simply heated with aqueous sulfuric acid, effecting hydrolysis to give exclusively **6** as the product. Total overall isolated yields for the conversion of **8** to **6** were typically in the 85−90% range.

Attempts to remove a second fluorine by treatment of **5** under the reaction conditions were unsuccessful; no difluorinated products could be obtained, despite forcing conditions. This result is in contrast to the results from the hydrodechlorination of **2**, whereby one, two, or three chlorine atoms could be removed in succession depending upon the reaction conditions.[15]

(14) Kamai, S. Jpn. Kokai Tokkyo Koho JP 02/145538, 1990; *Chem. Abstr.* **1991**, *113*, 152040c.

The defluorination reaction conditions developed in these labs appear to be specific to N-substituted phthalimides. Treatment of other protected phthalic acids such as tetrafluorophthalonitrile with conditions developed by us (zinc and aqueous sodium hydroxide) caused rapid hydrolysis leading to tetrafluorophthalic acid. It is known that this compound will not undergo defluorination but instead, under the reaction conditions, will lead to phenolic type products, as shown below.[16]



Improvements in the Imidization of 7. The second challenge overcome in the process optimization was an improvement in the preparation of **8**. This was achieved by developing the imidization of **2** in *commercial grade* sulfolane, thereby eliminating the need for glacial acetic acid as a solvent. The use of sulfolane had the advantage of being the same solvent needed for the next step in the reaction; thus a costly solids isolation step was also eliminated. Simply sparging anhydrous methylamine into a hot solution of **2** in sulfolane led to a clean conversion to **7** in isolated yields of around 90%.

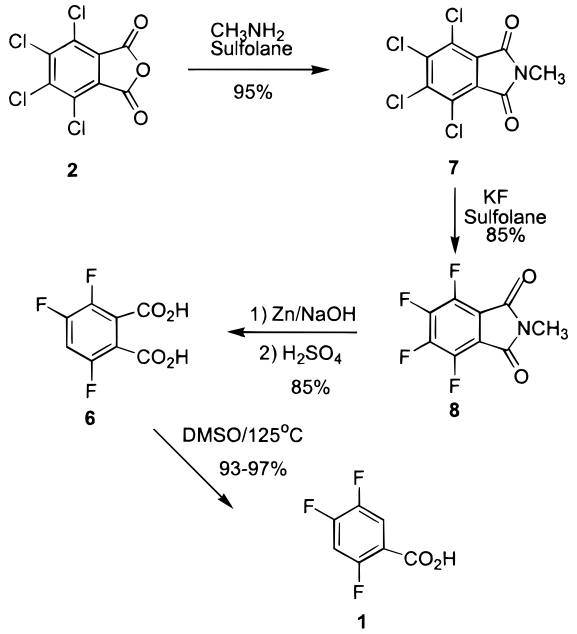
In practice, however, **7** was not isolated. The water formed during the imidization reaction could be simply removed by distillation, and the resultant solution of **7** (in *dry* sulfolane) was then ready for the halogen-exchange reaction to **8** utilizing spray-dried potassium fluoride.[1,8] The sulfolane could be eventually recycled back to the imidization reaction with a minimum of loss. It was important to keep the amount of methylamine added to the reaction mixture as close as possible to the theoretical amount. Any excess led to byproducts (presumably *N*-methylanilines via displacement of chloride on the ring) which led to lower yields in the halogen-exchange reaction.

The success of the defluorination reaction, in terms of both yield and selectivity, made it a promising alternative which could be incorporated into a new synthesis of **1**. The sequence of chemical steps for the new synthetic route was strikingly similar to the older hydrodechlorination route.[1,4] The only differences, besides incorporation of the new hydrodefluorination reaction in place of the hydrodechlorination reaction, were (a) the imidization of **2** to **7** instead of **3** to **4** and (b) the halogen-exchange reaction of **7** to **8** instead of **4** to **5**. However, despite the similarity in the chemistry, the effect on the yield was anything but similar. The *overall*

(15) Fertel, L. B.; Callaghan, K. M., O'Reilly, N. J. *J. Org. Chem.* **1993**, *58*, 261.

(16) Kikuo, A.; Masayoshi, O. U.S. Patent 4,813,190, 1989.

Scheme 2. **Revised route to 1**



yield of **1** from **2** was increased from 35% to 60%. The revised process is summarized in Scheme 2.

Conclusion

We have accomplished a synthesis of 2,4,5-trifluorobenzoic acid (**1**) in a 60% overall yield over five steps. Central to the success of this venture was the development of an effective, high-yielding selective hydrodefluorination/hydrolysis reaction of **8** to **6**. In addition, the use of sulfolane as a solvent in the formation of **7** led to elimination of acetic acid as a solvent and an elimination of a costly solids isolation step. The combination of these two reaction sequences led to a mixture of products with the right regiochemistry to carry on to **1**. The reaction conditions developed appeared to be specific for N-substituted phthalimides. The procedure as developed is suitable for scale-up: we have successfully applied this synthetic sequence in synthesizing 50−100-kg quantities of **1** in a pilot plant operation.

Experimental Section

^{19}F and ^{1}H NMR spectra were run on a Brucker AC 200-MHz spectrometer. All spectra were run at 295 K. For fluorine spectra, hexadeuterioacetone was used as the solvent and 4-fluoronitrobenzene was used as the internal standard (−103.6 ppm). Mass spectra were recorded on either a Finnegan MAT 212 or 4500 or Hewlett-Packard 5985 mass spectrometer. Melting points were determined on a Büchi 510 melting point apparatus. Reactions were followed on a 30-m DB-5 capillary column installed on a Hewlett-Packard 5890 series II gas chromatograph. Chemicals were purchased from the Aldrich Chemical Co. and were used without purification. Spray-dried KF was purchased from Aldrich Chemical and was dried for 2 days at 300 °C under 0.1 mmHg vacuum. Zinc dust (grade 64) was purchased from the New Jersey Zinc Company. Sulfolane was purchased from Phillips and used without further purification.

Preparation of 3,4,5,6-Tetrachloro-*N*-methylphthalimide (7). Into a 5-L, three-neck round-bottom flask equipped with a mechanical stirrer, a Teflon gas addition tube, a thermometer, and a dry ice condenser containing acetone/dry ice were charged **2** (500 g, 1.7 mol) and 2 kg of sulfolane. Anhydrous methylamine (52.6 g, 1.7 mol) was slowly added subsurface through the addition tube over a 2-h time period. The temperature of the reactor increased from 25 to 43 °C during the addition; a cooling bath was needed to keep the temperature within this range. The contents were then heated to 110 °C and held at that temperature for 2.5 h. Analysis of the reaction mixture by GC showed 99.2% conversion to **7**. The dry ice condenser was removed, a short-path distillation head was attached, and a vacuum (18−20 mmHg at a pot temperature of 158−160 °C) was applied to distill off water formed during the imidization (30.6 g). A total of 97 g of distillate (water and sulfolane) was collected. The pot contents were then ready for the halogen-exchange reaction as described previously.[1]

Hydrodefluorination of 8. In a 100-mL single-neck flask with a condenser and a magnetic stirrer were charged **8** (10.0 g, 0.0429 mol), zinc dust (11.2 g, 0.1718 mol) and aqueous sodium hydroxide (50 mL of a 10% w/w solution). The reaction mixture was heated at 75 °C for 2.5 h, at which time the reaction mixture was cooled to room temperature. The zinc salts were filtered off and washed with a small amount of water. The filtrate was then acidified with concd HCl to a pH of 0.5−1.0 and extracted with ethyl acetate (4 × 75 mL). The organics were dried over $MgSO_4$ and then removed under vacuum. A total of 10.14 g of solids was recovered. An assay of the solids by GC/MS indicated that 79.2% was **5** ($M^+ = 215$) and 15.1% was **10** ($M^+ = 202$). Upon further analysis by ^{19}F NMR, it was found that the open form of **5** had been formed (**11** or **12**) as well as **6**. For **11** or **12**: ^{19}F NMR (acetone-d_6/4-fluoronitrobenzene) $\delta =$ −115.7 (m, 1 F), −131.2 (m, 1 F), −143.9 (m, 1 F). For **6**: ^{19}F NMR (acetone-d_6/4-fluoronitrobenzene) $\delta = -112.9$ (m, 1 F), −128.7 (m, 1 F), − 143.6 (m, 1 F).

Preparation of 3,4,6-Trifluorophthalic Acid (6). The above solids mixture was placed in a 50-mL single-neck flask equipped with a condenser and a magnetic stir bar. Sulfuric acid (25 mL of a 65% aqueous solution) was added, and the reaction mixture was heated to 150 °C for 7 h. After cooling to room temperature, 150 mL of water was added. The mixture was extracted with ethyl acetate (4 × 50 mL) and dried over $MgSO_4$. After removal of the drying agent by filtration, the solvent was removed under vacuum, leaving 8.25 g of a solid, identified as **6** by comparison to an authentic sample.[1] GC analysis of the solid indicated that a small amount of **1** had been formed (ca. 5%). The overall yield from tetrafluorophthalimide **8** to trifluorophthalic acid **6** was 87%.

Preparation of 6 by Single-Step Hydrodefluorination/Hydrolysis. In a 1-L, three-neck round-bottom flask equipped with a mechanical stirrer, a condenser, and a thermometer were combined water (264 mL) and NaOH (50.95 g). The solution was allowed to cool to room temperature, at which time **8** (132.03 g, 0.57 mol) was added, followed by

portionwise addition of zinc dust (111.26 g, 1.7 mol). After a mild exotherm had subsided (cooling in an ice bath was necessary to keep the internal temperature at 60 °C), the mixture was stirred and heated at 60 °C for 1.5 h. The zinc salts were filtered while warm and washed with water (3 × 50 mL). The filtrate, a light yellow hazy solution, was immediately transferred into a second 1-L, three-neck flask equipped with a mechanical stirrer, an addition funnel, and a thermometer. Aqueous sulfuric acid (62.24 g of a 60% (w/w) solution) was added dropwise, followed by heating at 80 °C for 1 h. After cooling to room temperature, some solids precipitated out of solution and were filtered off, washed with cold water (3 × 25 mL), and dried; 39.44 g of **6** was recovered (purity >99% by GC). The filtrate was extracted with ethyl acetate (3 × 100 mL), and the combined organics were washed with water (2 × 50 mL) and saturated NaCl. After drying over $MgSO_4$, the solvent was removed and the resultant solids were pumped dry; 80.86 g of **6** was recovered (purity 89.5%). The total yield of recovered **6** was 120.3 g (89.8% total yield of **6**, accounting for purity). The melting point and spectral properties were identical to those of an authentic sample of **6**.[1]

Acknowledgment

Thanks to Bill Derwin for expert experimental assistance.

Received for review September 29, 1997.

OP970244C