Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

An Improved Large-Scale Preparation of Benzimidazole-2-Sulfonic Acids and 2-Chlorobenzimidazoles.

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Version of record first published: 22 Aug 2006

SYNTHETIC COMMUNICATIONS, 28(9), 1703-1712 (1998)

AN IMPROVED LARGE-SCALE PREPARATION OF BENZIMIDAZOLE-2-SULFONIC ACIDS AND 2-CHLOROBENZIMIDAZOLES.‡

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Abstract

An improved method for the preparation of benzimidazole-2-sulfonic acids from 2-mercaptobenzimidazoles has been developed which utilizes aqueous sodium percarbonate. 2-Chlorobenzimidazoles were obtained in high yield from the corresponding sulfonic acids upon reaction with PCl_5 in $POCl_3$ on a gram-mole scale.

Introduction

Over the years, a significant part of our research efforts have been directed towards the synthesis of certain 2-chlorobenzimidazole nucleosides[1,2] and non-nucleosides[3] as potential chemotherapeutic (antineoplastic, antiparasitic and antiviral) agents. This research prompted us to devote considerable time and effort

‡ Dedicated to Henry Koppel.

in attempts to devise a method that would allow us to prepare the requisite 2-chlorobenzimidazoles, specifically 2-chlorobenzimidazole, 2,5-dichlorobenzimidazole and 2,5,6-trichlorobenzimidazole, in quantities of several hundred grams. Although a significant number of 2-chlorobenzimidazoles are known,[4] the introduction of a chloro group at the C-2 position of benzimidazole is not readily accomplished. Many of these compounds were obtained in low to moderate yields from a reaction of the corresponding benzimidazol-2-one with phosphorus oxychloride ($POCl_3$) at reflux temperature,[4] during which anhydrous hydrogen chloride may be added.[5] Chlorination at C-2 becomes especially difficult when the benzene ring is substituted with halogens, usually resulting in very low yields.[6,7] Thus, this method for the preparation of 2-chlorobenzimidazoles with halogen substitutents on the benzene ring is of limited preparative value.

Oxidation of a benzimidazole-2-thione to the corresponding sulfonic acid, followed by a reaction with phosphorus pentachloride (PCl_5), has been shown to yield 2-chlorobenzimidazoles.[8,9] Balli and Kersting[8] obtained 1-ethyl-2-chlorobenzimidazole in 69% yield from 1-ethyl-2-benzimidazolesulfonic acid on reaction with PCl_5 in $POCl_3$ at reflux temperature. This methodology apparently has had minimal use. However, we reasoned that it could be extended to the large-scale preparation of the 2-chlorobenzimidazoles that we required.

Benzimidazole-2-thiones are readily available, either commercially or by preparation from the requisite o-phenylenediamines on reaction with potassium ethylxanthate.[10] Oxidation of benzimidazole-2-thione with $KMnO_4$ in aqueous base[11] or 30% hydrogen peroxide in aqueous base[12] gives benzimidazole-2-sulfonic acid in 90% yield. On scale up, however, oxidation with $KMnO_4$ has certain practical limitations due to the necessity of removing large quantities of finely divided MnO_2 before the product can be isolated. From this standpoint, the oxidation with 30% hydrogen peroxide is preferred since the isolation of product is

straightforward. Unfortunately, a large scale application is limited due to the inherent safety precautions required in handling large quantities of hydrogen peroxide.

Recently, Ando et al.[13] reported the preparation of diphenyl sulfone and dibenzyl sulfone in high yields by the oxidation of the corresponding thioethers with sodium percarbonate ($NaCO_3 \cdot 3/2\ H_2O_2$). Sodium percarbonate is a safe and easily handled solid form of hydrogen peroxide.[14] The oxidation of heterocyclic mercaptans to sulfonic acids with this reagent does not appear to have been reported.[14] However, it was apparent, to us, that sodium percarbonate would offer a viable alternative to 30% hydrogen peroxide as an oxidant for the large scale preparation of benzimidazole-2-sulfonic acids. We found that when a suspension of benzimidazole-2-thione (**1a**), on a 20 mmol scale, in an aqueous solution of sodium percarbonate was slowly heated to reflux, oxidation proceeded smoothly, and the corresponding benzimidazole-2-sulfonic acid (**2a**) was obtained in 65% yield. Scaling up this oxidation of **1a**, with sodium percarbonate, to 100 mmol gave an 85% yield of **2a**. Isolation and purification of **2a** was straightforward giving a high recovery of purified material. 5-Chlorobenzimidazole-2-sulfonic acid (**2b**) was also prepared in 83% yield. The scale up posed no problems and several hundred grams of 5,6-dichlorobenzimidazole-2-sulfonic acid (**2c**) were prepared in a single reaction with a yield of 92%. Since this reaction is facile and convenient, we suggest that this should be a preferred procedure for the oxidation of benzimidazole-2-thiones to benzimidazole-2-sulfonic acids.

For reactions of benzimidazole-2-sulfonic acids with PCl_5 in $POCl_3$, it was found that a ratio of 2-3 moles of PCl_5 per mole of sulfonic acid is most efficient. Phosphorus oxychloride serves as a solvent and the amount of this solvent can be limited to the volume required to effect efficient stirring. The initial reaction of the

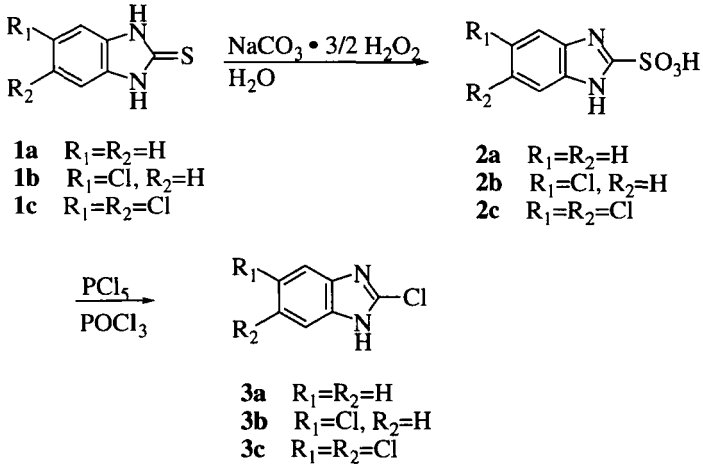
benzimidazole-2-sulfonic acid with PCl_5 is highly exothermic, becoming violent as the reflux temperature is reached. This condition lasts for a short period of time (approx. 15 min.) then subsides giving an intermediate of unknown structure. Continued heating of this mixture at reflux temperature for a minimum of four hours resulted in product formation. Copious amounts of SO_2 and HCl are evolved. However, with precautions taken to scrub the effluent,[15] several hundred grams of product can be prepared in a single run. We were pleased to find that yields for the preparation of 2-chloro- (**3a**), 2,5-dichloro- (**3b**), and 2,5,6-trichlorobenzimidazole (**3c**) were excellent with the workup of the reaction and purification of product being straightforward. Both the oxidation and chlorination reactions have been performed on small and large scale. Although we report only the preparation of 2-chlorobenzimidazole, 2,5-dichlorobenzimidazole, and 2,5,6-trichlorobenzimidazole, we have also prepared other 2-chlorobenzimidazoles by this route with similar results.

In summary, we have developed an improved method for the large-scale preparation of benzimidazole-2-sulfonic acids by the oxidation of benzimidazole-2-thiones with sodium percarbonate. Reactions of benzimidazole-2-sulfonic acid, 5-chlorobenzimidazole-2-sulfonic acid, and 5,6-dichlorobenzimidazole-2-sulfonic acid with 2-3 moles of PCl_5 in $POCl_3$ at reflux temperature give the corresponding 2-chlorobenzimidazoles in high yields.

Experimental

General Procedures. Sodium percarbonate was purchased from Fluka AG. Benzimidazole-2-thione, 5-chloro-1,2-phenylenediamine, 4,5-dichloro-2-nitroaniline, $POCl_3$, and PCl_5 were obtained from Aldrich Inc. Benzimidazole-2-thione was reprecipitated before use. 4,5-Dichloro-2-nitroaniline was reduced to 4,5-dichloro-1,2-phenylenediamine by the method of Acheson et al.[17,18] 5-

Scheme 1. Synthesis of benzimidazole-2-sulfuonic acids and the corresponding 2-chlorobenzimidazoles.



1a $R_1=R_2=H$
1b $R_1=Cl$, $R_2=H$
1c $R_1=R_2=Cl$

2a $R_1=R_2=H$
2b $R_1=Cl$, $R_2=H$
2c $R_1=R_2=Cl$

3a $R_1=R_2=H$
3b $R_1=Cl$, $R_2=H$
3c $R_1=R_2=Cl$

Chlorobenzimidazole-2-thione[19] and 5,6-dichlorobenzimidazole-2-thione[20] were prepared according to the method of Van Allen and Deacon.[10,21] Reactions described herein were performed in flasks of specified size fitted with an overhead stirrer, a heating mantle, and a condenser connected either to a gas bubbler or an acid gas scrubber. Large volume reaction mixtures were concentrated under reduced pressure (water aspirator) using a Buchi R-151 rotary evaporator. Products were dried to a constant weight in a vacuum drying oven under reduced pressure (water aspirator) and specified temperature. Melting points (uncorrected) were obtained on a Laboratory Devises Mel-Temp melting point apparatus. Thin layer chromatography was done using Analtech GHLF SiO_2 prescored plates and the specified solvent systems and visualized under ultraviolet light (254 nm). Proton magnetic resonance (^{1}H-NMR) spectra were obtained with a Brucker WP270SY spectrometer (solutions in DMSO-d_6) with the chemical shifts reported in parts per million downfield from tetramethylsilane as the internal standard.

Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of Michigan, Ann Arbor, MI.

The following are representative procedures for the preparation of benzimidazole-2-sulfonic acids and 2-chlorobenzimidazoles. The scale can be adjusted accordingly.

5,6-Dichlorobenzimidazole-2-sulfonic Acid (2c). General Method.

Water (6.5 L) and sodium percarbonate (607.1 g, 3.48 mol) were added to a 22 L three neck reaction flask, fitted with an overhead stirrer, a condenser connected to a gas bubbler, and a heating mantle. After a solution was obtained, 5,6-dichlorobenzimidazole-2-thione (**1c**, 380.5 g, 1.74 mol) was added in portions over one hour to avoid an excessive exothermic reaction. Once addition was completed and the initial exothermic reaction had slowed, the mixture was heated at reflux temperature until gas evolution had ceased (4 hr) and no starting material was detected by TLC.[22] The resulting solution was allowed to cool to ambient temperature, treated with activated charcoal, and filtered through a pad of Celite. The filter pad was washed with water (2 x 500 mL) and discarded. The clarified solution was carefully acidified to pH 1 with conc. HCl (600 mL, 7.2 M) which gave a precipitate. The mixture was allowed to stand at 5 °C for 24 hr. The solid was collected by filtration, washed with water, and redissolved in a solution of sodium carbonate (184.0 g) in water (6 L). The resulting solution was again treated with activated charcoal, filtered through a pad of Celite, and acidified by the careful addition of conc. HCl (500 mL) to reprecipitate the product. After storing at 5 °C for 18 hr, the solid was collected by filtration, washed with water, and dried at 75 °C under reduced pressure to give 429.3 g (92%) of 5,6-dichlorobenzimidazole-2-sulfonic acid as a white solid. mp. 362-364 °C (eff); ^{1}H-NMR (DMSO-d_6) δ 7.92 (s, H-4, H-7). Anal. Calcd. For $C_7H_4N_2Cl_2SO_3 \cdot H_2O$: C, 29.49; H, 2.12; N, 9.83. Found: C, 29.72; H, 2.15; N, 9.90.

Benzimidazole-2-sulfonic acid (2a).

The reaction of benzimidazole-2-thione (**1a**, 3.01 g, 0.02 mol.) with sodium percarbonate (6.28 g, 0.04 mol.) in water (50 mL) gave 2.56 g (65%) of benzimidazole-2-sulfonic acid (**2a**). mp 374-376 °C. (lit.[11] mp 365-366 °C); ^{1}H-NMR (DMSO-d_6) δ 7.57 (m), 7.72 (m).

5-Chlorobenzimidazole-2-sulfonic acid (2b).

The reaction of 5-chlorobenzimidazole-2-thione (**1b**, 36.9 g, 0.2 mol.) with sodium percarbonate (78.5 g, 0.5 mol.) in water (900 mL) gave 38.4 g (83%) of 5-chlorobenzimidazole-2-sulfonic acid (**2b**). mp 381-382 °C (eff. and dec). (lit.[12] mp >340 °C); ^{1}H-NMR (DMSO-d_6) δ 7.60 (d, H-7), 7.72 (d. H-5), 7.75 (s, H-4), 9.75 (bs).

2,5,6-Trichlorobenzimidazole (3c). General Method.

A twelve liter reaction flask was fitted with an overhead stirrer, a heating mantle, and an oversized condenser[23] connected to an acid gas scrubber. The flask was charged with $POCl_3$ (1 L) and PCl_5 (838.3 g, 4.0 M). 5,6-Dichlorobenzimidazole-2-sulfonic acid (**2c**, 429.3 g, 1.61 M) was added in portions to avoid excessive gas evolution. Once addition was complete, the mixture was slowly brought to reflux temperature at which time an extremely vigorous exothermic reaction took place. The heat source was removed until this reaction had subsided (15 min.). The resulting paste was heated at reflux temperature for 6 hr giving a mobile suspension. This suspension was allowed to cool overnight to ambient temperature with protection from moisture. The suspension was hydrolysed by a careful addition to ice water (2 x 5 L)[24] with ice being added as needed. After hydrolysis was completed, conc. NH_4OH was added to bring the mixture to pH 5-6. The precipitate was collected by filtration, washed with water, and dried at 50 °C under reduced pressure for 48 hr to give 299.3 g (84%) of **3c** (mp 208-210 °C). The precipitate was suspended in 4 L of 1:1 (V:V)

CH_2Cl_2/cyclohexane and stirred for 2 hr. The solid was isolated and air dried to give 293.5 g (82%) of purified 2,5,6-trichlorobenzimidazole as a beige powder. mp. 219-221 °C (lit.[7] 233-234 °C dec); R_f = 0.8 (1:1 (V:V) EtOAc/Hexane, SiO_2); ^{1}H-NMR (DMSO-d_6) δ 7.81 (s, H-4, H-7). Anal. Calcd. For $C_7H_3N_2Cl_3$: C, 37.96; H, 1.36; N, 12.65. Found: C, 37.44; H, 1.62; N, 12.50.

2-Chlorobenzimidazole (3a).

The reaction of benzimidazole-2-sulfonic acid (**2a**, 99.1 g, 0.5 mol.) with PCl_5 (312.0 g, 1.5 mol.) in $POCl_3$ (250 mL) gave 61.2 g (80%) of 2-chlorobenzimidazole (**3a**). mp 186-188 °C and then resolidified (inserted at 178 °C) (lit.[6] 181 °C, softens and effervesces). ^{1}H-NMR (DMSO-d_6) δ 7.20 (m, 2H), 7.52 (m, 2H), 12.85 (bs, NH).

2,5-Dichlorobenzimidazole (3b).

The reaction of 5-chlorobenzimidazole-2-sulfonic acid (**2b**, 37.2 g, 0.16 mol.) with PCl_5 (66.6 g, 0.32 mol.) in $POCl_3$ (70 mL) gave 24.9 g (83%) of 2,5-dichlorobenzimidazole (**3b**). mp 202-204 °C (lit.[20] mp 200-201 °C); ^{1}H-NMR (DMSO-d_6) δ 7.22 (d, H-7), 7.52 (d. H-5), 7.59 (s, H-4), 13.49 (bs, NH).

Acknowledgment

The authors would like to thank Ms. Marina Savic for the preparation of this manuscript. These studies were supported by research grant U0I-AI31718 from the National Institute of Allergy and Infectious Diseases, Research Agreement DRDA 942941 with Glaxo-Wellcome Co., and NIH Training Grant T32-GM07767 from the National Institute of Health.

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15. The acid gas effluent can be scrubbed by continuous water flow as described in ref. 16.

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18. It was found that the best conditions for reduction were to use a minimum of 10 mL ethanol and 0.1 g of Raney nickel per gram of 4,5-dichloro-2-nitroaniline. By decreasing the volume of solvent the product precipitates on the catalyst.

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21. The reaction times for each compound respectively were 12 hr and 24 hr. It is recommended that potassium ethyl xanthate be prepared *in situ* and the benzimidazole-2-thiones be reprecipitated before use.

22. The solvent system used was $CHCl_3$:CH_3OH 10:1 (V:V). Benzimidazol-2-thiones typically have very high R_f Values (>0.8) in this system whereas the R_f values for the benzimidazole-2-sulfonic acids are very low (<0.2).

23. This is needed to control the initial extremely exothermic reaction that occurs on heating.

24. This is conveniently carried out by dividing the reaction mixture into two or three portions contained in 20 L plastic buckets. The time required for neutralization is reduced to approximately 2 hr.

(Received in the USA 02 November 1997)