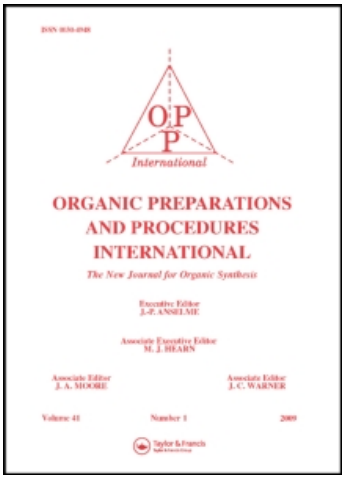

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AN EFFICIENT SYNTHESIS OF 4,4'-DIAMINODIPHENIC ACID

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OPPI BRIEFS

AN EFFICIENT SYNTHESIS OF 4,4'-DIAMINODIPHENIC ACID

Submitted (11/07/05)

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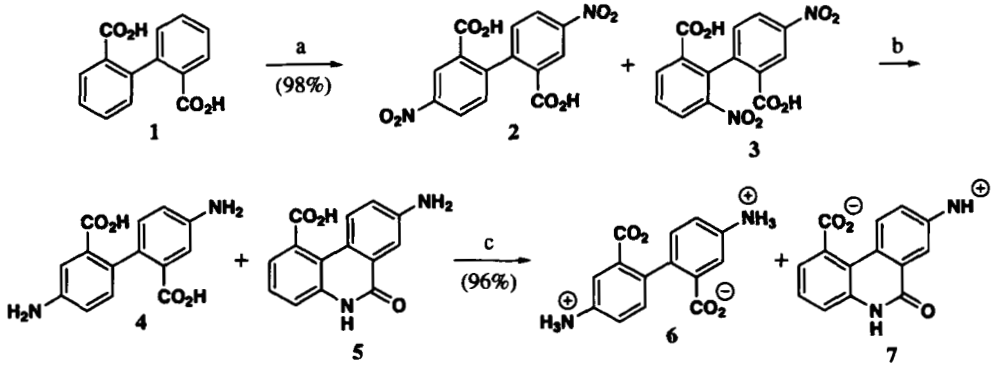
4,4'-Diaminodiphenic acid (DDPA, **4**) has received attention in recent years due to its importance for the synthesis of biologically active compounds[1] and in material science.[2] In particular, it is a key intermediate in the synthesis of polyamides,[3] polyesters,[4] photo-resists,[5] liquid crystals,[6] pigments and printing inks,[7] and also as a reagent in analytical chemistry.[8] Of the several reported DDPA preparations,[9,10] the direct nitration of diphenic acid **1**, followed by catalytic hydrogenation, appears acceptable.[10] However, the chromatography step and low overall yield of DDPA (25-27%) make this approach unsuitable for large scale syntheses. This article describes a novel, practical, and economical synthesis of **4** by a two-step procedure.

It was believed that, in the hydrogenation process, the amino group of 4,6'-diamino isomer (a minor component in the mixture) would undergo cyclization with the neighboring 2-carboxy group to give the intermolecular lactam **5** which should be easily separable from the desired 4,4'-diamino derivative **4** by careful control of the pH.

As a matter of fact, hydrogenation and chemical separation of the products were performed in a telescopic process. All steps may be carried out without isolation and purification of intermediates. After nitration, the mixture was poured into ice and allowed to warm to ambient temperature. The resulting suspension was neutralized with 10N aqueous NaOH to give



a solution of sodium salts which was hydrogenated. After hydrogenation, the basic reaction mixture was filtered through Magnesol®, and the mother liquor was titrated with glacial AcOH. At pH 5.29-6.06, the zwitterion **6** of the 4,4'-diaminodiphenic acid (**4**) precipitated as a grayish-white crystals while the zwitterion **7** of lactam **5** settled from the mother liquor as white solid at pH 3-4 (titration with 1N aqueous HCl). Sixty-two grams of 4,4'-diaminodiphenic acid zwitterion (**6**) and 18 g of the lactam zwitterion (**7**) were isolated starting from 100 g of diphenic acid **1**. The overall conversion to **6** and **7** is 94%. The structure of the 4,4'-diaminodiphenic zwitterion **6** was established by conversion to the corresponding dimethyl ester and comparison with an authentic sample.[11]

EXPERIMENTAL SECTION

2,2'-Diphenic acid (98% purity) and 10 wt. % Pd/C, Degussa type E101 (water ~50%) were purchased from Aldrich Chemical Co. 30/40 Magnesol® is available from BNL. Hydrogenation was carried out in 2 L Parr reactor; TLC was performed on Kieselgel 60 F_{254} (Merck) plate using EtOAc-heptane (1:1 v/v) as eluent. Melting points were determined on a Thomas Electro thermometer. Elemental analyses were carried out by the Analytical Laboratory, Wyeth, Pearl River, NY.

4,4'-Dinitro-2,2'-diphenic Acid (2) and 4, 6'-Dinitro-2, 2'-diphenic Acid (3).- To a mixture of 90% HNO_3 (750 mL) and conc. H_2SO_4 (250 mL) were added at 0°C the small portions of 2,2'-diphenic acid (**1**) (100.0 g, 0.412 mol) over about 2 h. At this point TLC showed no starting material but only the 4, 4'-dinitro isomer (R_f 0.63) and the 4, 6'-dinitro isomer (R_f 0.36). The reaction mixture was poured onto crushed ice (1.5 kg). The white precipitate was collected, washed with water, acetone and dried to give 125.7 g (98%) of mixture **2** and **3** which was used for hydrogenation without further purification.

4,4'-Diamino-2,2'-diphenic Acid (4) and 3-Amino-5,6-dihyrobenzo[c]qhinolin-10-carboxylic Acid (5).- A solution of **2** and **3** (125.7 g) in 1 L of water (pH 2.78) was basified with 10 N NaOH to pH 8.5. This solution was hydrogenated at 50 psi of H_2 for 1.5 h in the presence of 10% Pd/C. When the reduction was completed (TLC control), the mixture was filtered through Magnesol·. The filtrate (pH 9.36) was used for the isolation of **6** and **7** as described below.

4,4'-Diamino-2,2'-diphenic Acid (6, *zwitterion*) and Lactam (7, *zwitterion*).- The filtrate from the previous experiment was acidified very slowly by titration with AcOH. At pH 5.29, light grey crystals began to appear. The mixture was stirred for 1 h, after which time the pH rose to 6.06. More AcOH was added to adjust pH to 5.3, and again the mixture was stirred for 1 h. The crystals were collected, washed with water and acetone and then dried to give 62.0 g (55%) of light grey solid of 99.3% purity (HPLC area%), mp. > 230°C (dec.), *lit.*[11] mp. 265°C.

Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76, H, 4.41, N, 10.29. Found: C, 61.97, H, 4.43, N, 10.13.

The clear filtrate from above was acidified to pH ~3 with 1N HCl. The resulting white solid (**7**) was collected, washed with water, acetone and dried to give 18.0 g (17%) of colorless solid, mp. > 300°C (dec.), *lit.*[10] mp. 330-335°C.

Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14, H, 3.94, N, 11.02. Found: C 65.94, H, 3.87, N, 10.86.

Dimethyl 4,4'-Diamino-2,2'-diphenoate.- A mixture of **6** (5.0 g, 0.018 mol), MeOH (25 mL) and conc. H_2SO_4 was refluxed for 48 h with TLC monitoring of the disappearance of starting material, appearance and disappearance of monoester and accumulation of the desired diester. When reaction was complete, the reaction mixture was poured into water, basified to pH ~10 with 20% aqueous NH_4OH and extracted with CH_2Cl_2. The organic phase was dried over $CaSO_4$ and evaporated to give 4.5 g (82%) of dimethyl 4,4'-diamino-2,2'-diphenoate as a colorless solid, mp. 103-106°C, undepressed upon admixture with an authentic sample.[12]

Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 64.00, H, 5.33, N, 9.33. Found: C, 64.34, H, 5.42, N, 9.05.

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12. A sample of dimethyl 4,4'-diaminodiphenoate for comparison was kindly supplied by S. Strunk of Wyeth.

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A CONVENIENT, ONE-POT SYNTHESIS OF THIOCARBAMATES USING *bis*(TRICHLOROMETHYL) CARBONATE

Submitted by (11/11/05)

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Thiocarbamates are an important class of compounds due to their biological activity[1] and have found wide applications in the chemical industry such as in the production of commodity chemicals such as herbicides,[2] pesticides,[3] bactericides[4] and antiviral agents.[5] Therefore the development of methods for the synthesis of thiocarbamates is important.

Several methods for the preparation of thiocarbamates have been reported in the literature[6] such as the reaction of amines with phosgene and thiols.[7] In addition, the direct condensation of thiols with carbamoyl chlorides[8] or isocyanates[9] has also been reported. Unfortunately, both carbamoyl chlorides and isocyanates are typically prepared from phosgene and some of them are difficult to store, as they are sensitive to water. There are a variety of other methods including (i) the reaction of carbon monoxide, amines with thiols[10] or disulfides[11] in the presence of metal catalysts, (ii) the use of sulfur[12] with amines and carbon monoxide followed by addition of alkyl halides, (iii) coupling of thiocyanates and alcohols in the presence of sulfuric acid,[13-14] (iv) the conversion of various *o*-substituted thiocarbamates *via* intramolecular rearrangement.[15] Recently, Wynne reported a synthesis of thiocarbamates from thiols[16] in which two equivalents of trichloroacetyl chloride and of amines were required. Despite of the numerous routes, most methods involve unstable reagents, multi-step procedures, harsh reaction conditions, expensive catalyst or complex materials. Base on these premises, we now report a mild and convenient one-pot procedure for the synthesis of thiocarbamates using *bis*(trichloromethyl) carbonate (BTC).

BTC is well known as an important equivalent for phosgene and has emerged as a versatile synthetic auxiliary in the preparation of various organic compounds.[17] Reactions with BTC usually proceed under relatively mild conditions and often afford good to excellent yields. The present work reports the reaction of BTC for the synthesis of thiocarbamates from thiophenols and amines.