An Efficient One-Pot Synthesis of Aminobenzimidazoles

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Received 28 June 2004; revised 13 September 2004

Abstract: An efficient one-pot procedure for the preparation of aminobenzimidazoles from dinitroaniline derivatives is described. The process helps to avoid the troublesome acetonitrile-mediated reductive ethylation reaction.

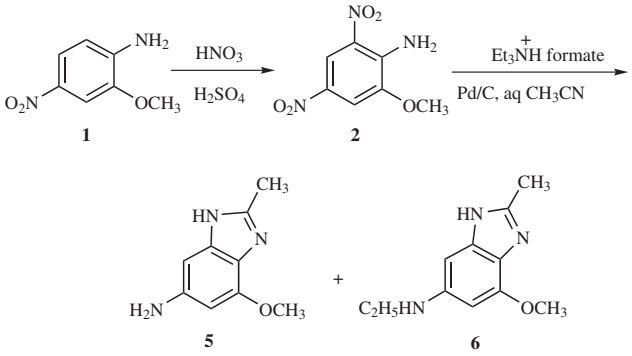
Key words: benzimidazoles, pyrroloquinoline quinines, reductive ethylation, bicyclic compounds, fused ring systems

Recently we reported the synthesis of several imidazole ester analogs of the important vitamin cofactor pyrroloquinoline quinone (PQQ).[2] These syntheses proceeded from commercially available benzene derivatives through 4,6-disubstituted benzimidazole intermediates, which were also potentially important physiologically active compounds.[3]

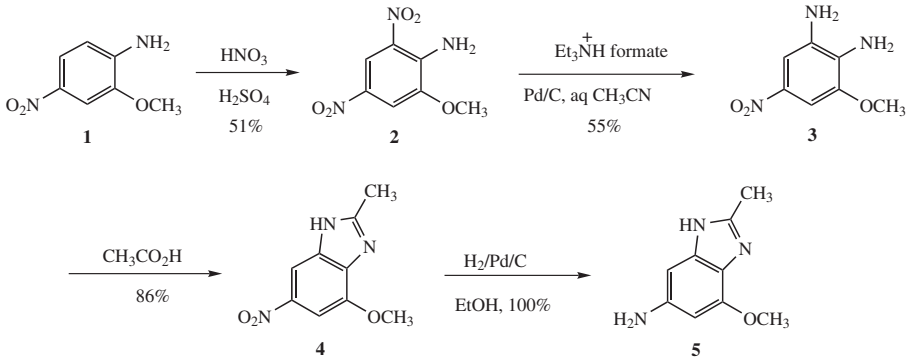
The synthesis of the benzimidazole **5** (Scheme 1) proceeded from the known 2-amino-3-methoxy-5-nitroaniline (**3**) in two steps by ring-forming condensation with acetic acid and hydrogenation of the nitro group. While these two steps were accomplished in excellent overall yield (85%), the earlier steps which involved selective nitration of commercially available 2-methoxy-4-nitroaniline (**1**) followed by subsequent selective reduction of the *ortho*-nitro group in the dinitro intermediate **2** occurred in modest yield (28% overall). Nevertheless, the yield of benzimidazole **5** from the commercially available compound **1** was sufficient to carry out the earlier reported syntheses of PQQ analogs.[2] An earlier synthesis of compound **3** proceeded in three steps from 2,3,5-trinitroanisole with an overall reported yield of about 40%, after the inefficient synthesis of 2,3,5-trinitroanisole from commercially available 3,5-dinitroanisole.[4] No yield was given for the nitration reaction, which had also been reported earlier by Blanksma.[5]

To improve the synthesis of benzimidazole **5**, we developed an alternative strategy (Scheme 2) avoiding selective reduction of the *ortho*-nitro group in the dinitro intermediate **2** (Scheme 1) by carrying out the complete reduction of **2** to yield the triamino intermediate under conditions facilitating simultaneous formation of the imidazole ring. Refluxing compound **2** in the presence of triethylammonium formate and palladium on carbon in acetonitrile gave the desired benzimidazole in one step. However, large amounts of the ethylaminobenzimidazole **6** were also formed. The ratio of **6** to **5** was about 3:1.

Compound **6** resulted from the apparent initial acetonitrile-mediated reductive ethylation of the nitro group dur-



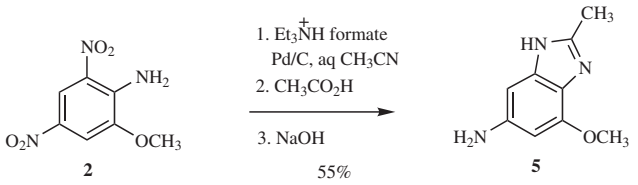
Scheme 2



Scheme 1

SYNTHESIS 2005, No. 1, pp 0017–0018
Advanced online publication: 17.11.2004
DOI: 10.1055/s-2004-834925; Art ID: M04604SS

ing or after reduction to the amine. By reducing the quantity of acetonitrile used to avoid the aminoethylation reaction, and completing the imidazole ring formation with acetic acid and hydrolyzing the acetanilide formed with aqueous sodium hydroxide, the synthesis of compound **5** could be completed in 55% yield in a one-pot procedure (Scheme 3). The acetanilide-benzimidazole intermediate was independently analyzed and characterized.



Scheme 3

In summary, the reduction of both nitro groups could be completed with simultaneous formation of the imidazole ring in an efficient one-pot process subsequent to selective nitration of the commercially available 2-methoxy-4-nitroaniline. This process should have general applicability to the synthesis of other amino-substituted benzimidazoles.

NMR spectra were recorded on a Varian 400 MHz spectrometer. Chemical shifts were expressed in ppm relative to TMS or the residual signal of deuterated solvent. For mixtures of tautomers, the ^{1}H NMR chemical shifts reported are for the major tautomer, whereas all ^{13}C chemical shifts are reported. Some ^{13}C NMR spectra presented fewer signals than expected and was attributed to scalar relaxation of the second kind due to the high number of nitrogen atoms present in the molecule. Crude yields are reported for products, which are, in general, greater than 90% pure based on NMR spectroscopy. Melting points are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, Georgia, U.S.A.

2-Methoxy-4,6-dinitroaniline (2)

A mixture of 2-methoxy-4-nitroaniline (**1**; 60 g, 0.357 mol), glacial AcOH (180 mL), and conc. H_2SO_4 (300 mL) was stirred mechanically until the solid had completely dissolved. The resulting solution was then cooled to 0 °C. A mixture of 70% HNO_3 (23.3 mL, 0.368 mol) and conc. H_2SO_4 (13.6 mL, 0.245 mol) was added slowly with constant stirring while maintaining the temperature below 10 °C. The reaction mixture was allowed to warm to r.t., stirred for 1 h, and poured onto crushed ice (1.5 kg). A solid precipitate was formed within 15–20 min, which was filtered and rinsed with cold water to yield a brown powder; yield: 39 g (51%). Recrystallization from CH_2Cl_2–hexane gave yellow crystals; R_f 0.73 (CH_2Cl_2); mp 173–176 °C (Lit.[6] mp 174 °C; Lit.[7] mp 181 °C).

^{1}H NMR ($CDCl_3$): δ = 4.06 (s, 3 H), 7.73 (d, 1 H, *J* = 2.7 Hz), 8.83 (d, 1 H, *J* = 2.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 56.99, 106.95, 115.61, 129.35, 135.91, 141.16, 147.77.

Anal. Calcd for $C_7H_7N_3O_5$: C, 39.73; H, 3.32; N, 19.72. Found: C, 40.05; H, 3.28; N, 19.38.

2-Amino-3-methoxy-5-nitroaniline (3)

To a solution of 2-methoxy-4,6-dinitroaniline (**2**; 8 g, 37.5 mmol) in a mixture of Et_3N (24 mL) and MeCN (20 mL) was added 10% Pd/C (370 mg). This suspension was cooled to 15 °C in a cold water bath. A solution of 96% formic acid (6.4 mL) in MeCN (20 mL) was then added over a period of 15 min while maintaining the temperature at 15 °C during the addition. The resulting mixture was then refluxed for 3 h. Completion of the reaction was monitored by TLC analysis (hexane–EtOAc, 1:1). The catalyst was removed by filtration through a silica gel plug and rinsed with acetone. The solvent was removed in vacuo, and the resulting solid mixture chromatographed on silica gel (hexane–EtOAc, 1:1) to yield 2-amino-3-methoxy-5-nitroaniline (**3**) as a red powder; yield: 3.80 g (55%). Recrystallization from absolute EtOH yielded dark orange crystals; R_f 0.50 (5% MeOH in CH_2Cl_2); mp 167 °C (Lit.[4] mp 165–167 °C).

^{1}H NMR (CD_3OD): δ = 3.89 (s, 3 H), 4.89 (s, 3 H), 7.29 (d, 1 H, *J* = 2.4 Hz), 7.38 (d, 1 H, *J* = 2.4 Hz).

^{13}C NMR (CD_3OD): δ = 56.52, 99.25, 106.81, 133.59, 134.31, 139.15, 146.90.

Anal. Calcd for $C_7H_9N_3O_3$: C, 45.89; H, 4.96; N, 22.94. Found: C, 45.95; H, 4.89; N, 22.82.

One-Pot Conversion of 2-Methoxy-4,6-dinitroaniline (2) to 6-Amino-4-methoxy-2-methyl-1*H*-benzimidazole (5)

2-Methoxy-4,6-dinitroaniline (**2**; 1.00 g, 4.69 mmol) and 10% Pd/C (250 mg) were suspended in a mixture of Et_3N (4.5 mL) and MeCN (3.75 mL) under argon. The flask was placed in a water bath at r.t., and a solution of 96% formic acid (1.8 mL) in MeCN (3.75 mL) was added dropwise. The mixture was then refluxed for 24 h, and cooled to r.t. The catalyst was removed by filtration and rinsed with MeOH and the solvent was removed in vacuo. Glacial AcOH (15 mL) was added to the residue and the resulting mixture was refluxed under argon for 12 h. The AcOH was then removed in vacuo and the residue was dissolved in aq 1 M NaOH solution (75 mL) and refluxed for 2 h. The mixture was then cooled to r.t., and the solution was brought to pH 10 with conc. HCl and evaporated to dryness. The residue was taken up in 10% MeOH in CH_2Cl_2 and passed through a silica gel plug to afford the product, after removal of solvent in vacuo; yield: 578 mg (68%). Full details on the characterization of this compound are given elsewhere.[2] The intermediate *N*-acetyl compound was recrystallized from EtOH in separate experiments.

***N*-(4-Methoxy-2-methyl-1*H*-benzimidazol-6-yl)acetamide**

R_f 0.14 (10% MeOH in CH_2Cl_2). Mp >300 °C.

^{1}H NMR (CD_3OD): δ = 2.12 (s, 3 H), 2.49 (s, 3 H), 3.92 (s, 3 H), 6.86 (br, 1 H), 7.42 (s, 1 H).

^{13}C NMR (CD_3OD): δ = 14.18, 23.97, 56.24, 98.83, 99.77, 126.79, 135.80, 140.09, 149.44, 152.28, 171.67.

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N 19.17. Found: C, 60.29; H, 6.00; N, 19.16.

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