Synthesis of 3,6-Dimethoxybenzene-1,2-diamine and of 4,7-Dimethoxy-2-methyl-1H-benzimidazole

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Received 11 December 2008; revised 19 February 2009

Abstract: Hydrogenation of a mixture of ortho- and para-dinitro derivatives of 1,4-dimethoxybenzene in ethyl acetate under palladium catalysis, allows 3,6-dimethoxybenzene-1,2-diamine to be isolated as the sole product; this diamine is then converted into 4,7-dimethoxy-2-methyl-1H-benzimidazole, a building block for the preparation of imidazobenz(hydro)quinones.

Key words: benzimidazoles, diamines, heterocycles, hydroquinones, reduction

Scheme 1

3,6-Dimethoxybenzene-1,2-diamine (1) is a synthon that has been used for the construction of aromatics, heterocycles, and quinones of both physical1,2 and biological3–5 relevance; 1 is obtained after nitration/reduction of 1,4-dimethoxybenzene (hydroquinone dimethyl ether) (Scheme 1 and Scheme 2). Since the first mention of this procedure,6,7 a dozen alternatives have been reported (Table 1 and Table 2), which suggest that some difficulties exist in its preparation. A close look at the described procedures led us to identify several points to be addressed as this could be of some help in establishing a reliable and high-yielding synthesis of 1. An efficient preparation of benzimidazole 2, which is a building block in the synthesis of imidazobenzoquinones,4 from 1 is also presented.

Nitration of 1,4-dimethoxybenzene has been performed using various methods and conditions to yield a mixture of ortho- 3 and para-isomers 4 (Scheme 3), the proportion of which depends on the experimental conditions (Table 1). The isolation of 3 in its pure state has been ef-

Scheme 2 3,6-Dimethoxybenzene-1,2-diamine as a synthon
fected by crystallization from ethyl acetate\cite{3,4,5} or from acetic acid,\cite{2,4} but, in our hands, using either solvent and starting with batches of different compositions, the enrichment of starting with a mixture of dinitro isomers \(1/_{4}\) was not proceeded beyond 90%.\cite{8,9} A chromatographic purification has also been proposed, but this necessitates large quantities of adsorbent (1 kg of silica gel for the purification of an 8 g mixture of \(3/4\)).\cite{4p}

With regard to the reduction step to diamine \(1\), several methods have been proposed (Table 2). Due to the ease of work-up,\cite{10} catalytic hydrogenation appears to be the method of choice and it has been performed under pressure in the presence of various catalysts (Table 2). As at atmospheric pressure, hydrogenation with palladium as catalyst has led to \(5\) and as it could be further reduced at atmospheric pressure,\cite{3b} "one-pot" conditions for full reduction to \(1\) were sought. Although the reduction of \(3/4\) at atmospheric pressure was slow (2–3 days), it could be driven to completion.\cite{11} During our search for optimal conditions, it was serendipitously discovered that, when the reduction was carried out in ethyl acetate, pure \(1\) could be isolated after mere filtration of the reaction mixture on Celite, followed by evaporation of the solvent.\cite{12,13} This avoids the indirect procedures that have been used for the isolation of \(1\)\cite{4e,4h} and sets up a high-yielding trouble-free preparation (83% from a 9:1 mixture of dinitro isomers; 96% based on \(3\)).

### Table 2 Reduction of Dinitro Derivatives \(3/4\)

| Entry | Substrate Conditions | Yield Ref. (%)
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>(3), (H_2), PtO(_2), EtOH</td>
<td>40 (4a)</td>
</tr>
<tr>
<td>2</td>
<td>(3), (H_2), Raney Ni, EtOH, 50 °C</td>
<td>60 (4c)</td>
</tr>
<tr>
<td>3</td>
<td>(3), Sn (14.5 equiv), concd HCl, 100 °C</td>
<td>56 (16d)</td>
</tr>
<tr>
<td>4</td>
<td>(3), Sn (5.8 equiv), 12 M HCl, 100 °C</td>
<td>98 (4p)</td>
</tr>
<tr>
<td>5</td>
<td>(3 + 4) (40:60), Sn, 12 M HCl, reflux</td>
<td>98 (4i)</td>
</tr>
<tr>
<td>6</td>
<td>(3 + 4) (89:11), SnCl(_2) (9.1 equiv), concd HCl, 90–100 °C</td>
<td>78 (4h)</td>
</tr>
<tr>
<td>7</td>
<td>(3 + 4) (H_2) (2–3 bar), Raney Ni, MeOH</td>
<td>12 (3a)</td>
</tr>
<tr>
<td>8</td>
<td>(3), NH(_2)NH(_2)-x H(_2)O, Raney Ni</td>
<td>55 (4f)</td>
</tr>
<tr>
<td>9</td>
<td>(3 + 4) Na(_2)S(_2)O(_4) (10 equiv), THF–MeOH (1:1), reflux</td>
<td>12 (3c)</td>
</tr>
<tr>
<td>10</td>
<td>(3 + 4) (H_2) (3.45 bar), PtO(_2), EtOH</td>
<td>62 (3c)</td>
</tr>
<tr>
<td>11</td>
<td>(3), (H_2) (5 bar), 10% Pd/C, EtOAc</td>
<td>99 (2)</td>
</tr>
<tr>
<td>12</td>
<td>(3 + 4) (H_2) (Parr apparatus), 10% Pd/C, AcOH</td>
<td>94 (16a)</td>
</tr>
</tbody>
</table>

\(a\) Mixture of two isomers (no ratio indicated), isolated as hydrochlorides.

\(b\) The crude product was used as such in the next step (yield is given for two steps).

\(c\) Ratio not available.

An indirect way to \(1\) consists of the selective reduction of \(3\) into \(5\), a compound that is easily purified,\cite{3b} which is followed by another reduction; however, this procedure adds an extra step. All of the above results explain why most of the syntheses presented in Scheme 2 were carried out starting with a mixture of dinitro isomers \(3/4\).
preparation, we found that performing the reaction under argon with freshly prepared 1 and using degassed acetic acid were decisive; this led to a reliable procedure, 2 being isolated in 96% yield.

Thus the preparations of 1 and 2 are now made simple and high yielding (74% and 71% overall yields, respectively, from 1,4-dimethoxybenzene), which thus improves previous procedures.

Pd/C was purchased from Acros (palladium on activated carbon unreduced 10%; specific area: 800 m²/g; particle size distribution: 90% < 90 μm). Reactions were monitored by TLC using Al-backed silica gel plates (Merck, Kieselgel 60 PF254); TLC spots were visualized under UV light and after spraying with 5% phosphomolybdic acid–EtOH followed by heating. NMR spectra were recorded on a Bruker Avance 300.12 spectrometer operating at 300.12 MHz (IH) and 75.47 MHz (13C); internal standards (δIH CHCl₃ = 7.26; δ13C CDCl₃ = 77.0). Elemental analyses were performed by the Service de Micro-Analyses, Département de Chimie Moléculaire, Grenoble.

1,4-Dimethoxy-2,3-dinitrobenzene (3) and 1,4-Dimethoxy-2,5-dinitrobenzene (4)

The nitration of 1,4-dimethoxybenzene was carried out according to ref. 2; crystallization (AcOH) afforded a mixture of 3 and 4 in 91:9 ratio.

ortho-Isomer 3

1H NMR (300 MHz, CDCl₃): δ = 3.92 (s, 6 H, OCH₃), 7.21 (s, 2 H, H₂, H₃).

para-Isomer 4

1H NMR (300 MHz, CDCl₃): δ = 3.97 (s, 6 H, OCH₃), 7.56 (s, 2 H, H₂, H₅).

3,6-Dimethoxybenzene-1,2-diamine (1)
The above mixture of 3 and 4 (4 g, 17.5 mmol) in EtOAc (80 mL) was stirred under a H₂ atmosphere (balloon) in the presence of 10% Pd/C (0.4 g) until the soln became colorless (2–3 d), at which stage removal of AcOH acid under reduced pressure, co-evaporation with Et₂O to afford pure 4,7-Dimethoxy-2-methyl-1H-benzimidazole (2). The above mixture of 1-H₁, 2-H₁, 3-H₁, 4-H₁, 5-H₁, 6-H₁, 7-H₁, 8-H₁, and 9-H₁.

4,7-Dimethoxy-2-methyl-1H-benzimidazole (2)

Argon was bubbled with stirring for 30 min through distilled AcOH (80 mL); this was then added to freshly prepared 1 (2.44 g, 12.7 mmol) and the soln was stirred under argon at 110°C for 15 h; after removal of AcOH acid under reduced pressure, co-evaporation with toluene was performed twice; the residue was then washed with Et₂O to afford pure 2 (2.52 g, 96%); mp 210°C (dec) (EtOH) (Lit. 4a, 224–226°C).

1H NMR (300 MHz, CDCl₃): δ = 2.62 (s, 3 H, 2-CH₃), 3.91 (s, 6 H, OCH₃), 6.54 (s, 2 H, H₄, H₅), 6.70 (s, 6 H, OCH₃), 7.21 (s, 2 H, H₂, H₃), 10.17 (s, 1 H, H₁).

4.7-Dimethoxy-2-methyl-1H-benzimidazole (2)


Acknowledgment

T.B. is grateful to the French ‘Ministère de l’Education Nationale, de la Recherche et de la Technologie’ for a doctoral fellowship.

References

(8) Ref. 7 reads that this is a co-crystallization process and that, provided there are no ‘small aggregates’, the separation of ‘rhombic plates’ from ‘long columns’ can be effected by hand.
(9) The ratio of isomers is determined by relative integration in $^1$H NMR spectra, for data see experimental.
(10) The mp recorded for this material is in the range of literature values (68–70 $^\circ$C,4e 75 $^\circ$C,7 85–87 $^\circ$C4a). Note that this material is labile: darkening with time of this electron-rich diamine has been noted previously and we found experimentally that even after minimal exposure to air, 1 became unreactive.
(11) A H$_2$-filled balloon is used, monitoring of the reaction can be performed by TLC or NMR (for data see experimental) but, most simply, it can be done by visual inspection as the mixture becomes colorless when reaction is complete.
(12) Hydrogenation of a 6:4 mixture of 3 and 4 was performed under the same protocol and, here also, only diamine 1 is isolated (51% yield; 85% based on 3).
(13) When the Celite pad was thoroughly washed with MeOH, 2,5-dimethoxybenzene-1,4-diamine was obtained together with minor unidentified material. The 2,5-dimethoxybenzene-1,4-diamine was identified spectroscopically, see: Miller, S. E.; Lukas, A. S.; Marsh, E.; Bushard, P.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7802.
(15) Impure 2 could not be freed from byproducts by crystallization or by chromatography, which furthermore led to severe losses of material.