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

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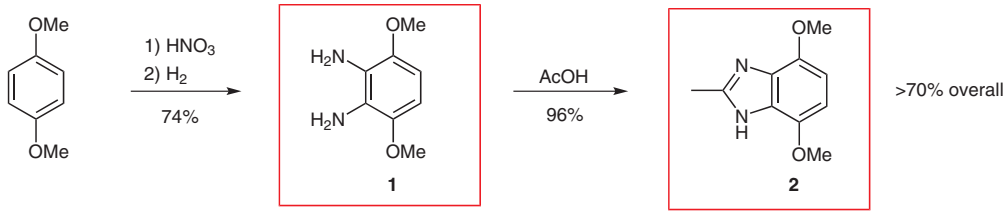
Received 11 December 2008; revised 19 February 2009

PSP No 158

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-1*H*-benzimidazole, a building block for the preparation of imidazobenzo(hydro)quinones.

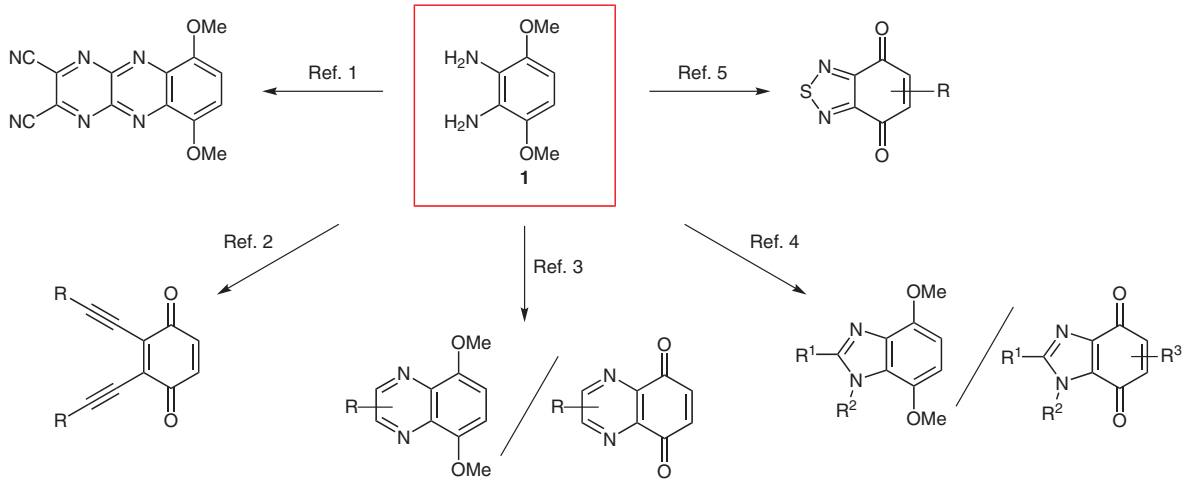
Key words: benzimidazoles, diamines, heterocycles, hydroquinones, reduction



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 physical[1,2] and biological[3–5] 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

SYNTHESIS 2009, No. 10, pp 1753–1756
Advanced online publication: 14.04.2009
DOI: 10.1055/s-0028-1088049; Art ID: T21708SS
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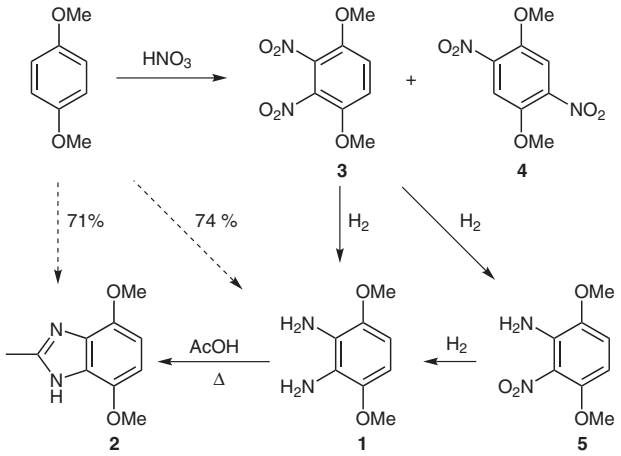
fected by crystallization from ethyl acetate[3a,6,7] or from acetic acid,[2,4a] but, in our hands, using either solvent and starting with batches of different compositions, the enrichment of **3** did not proceed beyond 90%.[8,9] A chromatographic purification has also been proposed, but this necessitates large quantities of adsorbent (1 kg of silica gel for the purification of an 8 g mixture of **3/4**).[4p]



Scheme 3 Preparation of **1** and **2**

Table 1 Nitration of 1,4-Dimethoxybenzene

Entry	Conditions	Ratio **3/4**	Yield (%)	Ref.
1	70% HNO_3, Ac_2O, 0 °C	45:55	95	4p
2	concd HNO_3, AcOH, r.t. then 70–80 °C	–[a]	80	3a
3	concd HNO_3, AcOH, r.t. then 90 °C	–[a]	80	3c
4	NO_2, O_3, CH_2Cl_2, –10 °C	54:46	81	16d
5	NO_2BF_4, DME, –50 °C	–[a]	76	16c
6	concd HNO_3, Ac_2O, 0 °C	–[a]	70	4f
7	concd HNO_3, 0–5 °C, 24 °C, then reflux	88:12[b]	91.6	16b
8	concd HNO_3, 0 °C, r.t., then 90 °C	89:11[b]	89	4h
9	62% HNO_3, 0 °C, r.t., then 100 °C	–[a]	90[c]	2
10	concd HNO_3, AcOH, r.t., 80 °C	–[a]	35[d]	16e
11	$Ag_{0.51}K_{0.42}Na_{0.07}NO_3 \cdot K_3Fe(CN)_6$ (4 equiv), 160 °C	45:55	35	16f

[a] Not available.
[b] Ratio from ^1H NMR and/or VPC.
[c] Yield of **3**.
[d] Yield of **4**.

An indirect way to **1** consists of the selective reduction of **3** into **5**, a compound that is easily purified,[3h] 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**.

With regard to the reduction step to diamine **1**, several methods have been proposed (Table 2). Due to the ease of work-up,[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,[3h] '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.[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.[12,13] This avoids the indirect procedures that have been used for the isolation of **1**[3c,g,4a] 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.
1	**3**	H_2, PtO_2, EtOH	40	4a
2	**3**	H_2, Raney Ni, EtOH, 50 °C	60	4c
3	**3**	Sn (14.5 equiv), concd HCl, 100 °C	56[b]	16d
4	**3**	Sn (5.8 equiv), 12 M HCl, 100 °C	98[a]	4p
5	**3** + **4** (40:60)	Sn, 12 M HCl, reflux	98	4j
6	**3** + **4** (89:11)	$SnCl_2$ (9.1 equiv), concd HCl, 90–100 °C	78[b]	4h
7	**3** + **4**[c]	H_2 (2–3 bar), Raney Ni, MeOH	12[b]	3a
8	**3**	$NH_2NH_2 \cdot x\ H_2O$, Raney Ni	55[b]	4f
9	**3** + **4**[c]	$Na_2S_2O_4$ (10 equiv), THF–MeOH (1:1), reflux	12	3c
10	**3** + **4**[c]	H_2 (3.45 bar), PtO_2, EtOH	62[b]	3c
11	**3**	H_2 (5 bar), 10% Pd/C, EtOAc	99	2
12	**3** + **4**[c]	H_2 (Parr apparatus), 10% Pd/C, AcOH	94[b]	16a

[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.

With **1** in hand, we looked for its conversion into **2**, a key building block for the preparation of imidazobenzoquinones.[4] The synthesis of **2** is based on the general method of Phillips,[14] which refers to the condensation of *ortho*-benzenediamines with carboxylic acids. Thus, reaction of **1** with acetic acid gives **2**,[4a,j,n] but our attempts to reproduce the described literature procedure led to impure **2** and only in fair yield.[15] During attempts to improve its

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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 m^2/g; particle size distribution: 90% < 90 μm). Reactions were monitored by TLC using Al-backed silica gel plates (Merck, Kieselgel 60 PF_{254}); 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 (^{1}H) and 75.47 MHz (^{13}C); internal standards (δ[^{1}H] $CHCl_3$ = 7.26; δ[^{13}C] $CDCl_3$ = 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**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 6 H, OCH_3), 7.21 (s, 2 H, H2, H3).

***para*-Isomer 4**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 6 H, OCH_3), 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 H_2 atmosphere (balloon) in the presence of 10% Pd/C (0.4 g) until the soln became colorless (2–3 d), at which stage TLC analysis or ^{1}H NMR showed the absence of intermediate **5** [R_f = 0.71, CH_2Cl_2, orange spot; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (2 s, 6 H, CH_3), 5.35 (br s, 2 H, NH_2), 6.16 (d, *J* = 8.9 Hz, 1 H, H4), 6.74 (d, *J* = 8.9 Hz, 1 H, H5)]. After filtration over a short pad of Celite and rinsing with a small amount of EtOAc (10 mL), the volatiles were removed under reduced pressure to afford **1** as the sole product (2.44 g, 83%, 96% based on **3**); **1** was flushed with argon and used immediately in the next step; mp 73–74 °C.[10]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.50 (br s, NH_2), 3.81 (s, 6 H, OCH_3), 6.31 (s, 2 H, H4, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9, 100.6, 124.6, 143.1.

4,7-Dimethoxy-2-methyl-1*H*-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 Et_2O to afford pure **2** (2.52 g, 96%); mp 210 °C (dec) (EtOH) (Lit.[4a] 224–226 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62 (s, 3 H, 2-CH_3), 3.91 (s, 6 H, OCH_3), 6.54 (s, 2 H, H4, H5), 6.70 (br s, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 55.9, 102.4, 129.9, 142.6, 149.4.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.25; H, 6.29; N, 14.58. Found: C, 61.97; H, 6.42, N, 14.78.

Acknowledgment

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

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(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 °C,[4e] 75 °C,[2] 85–87 °C[4a]). 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.
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