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FACILE PROTOCOL FOR THE SYNTHESIS OF ELECTRON-RICH BENZIMIDAZOLE DERIVATIVES

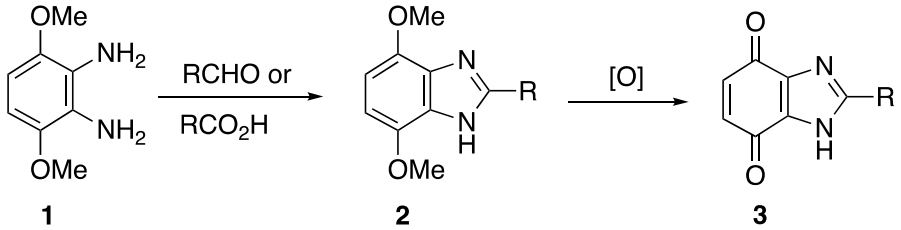
Robert D. Pike[a] and Brian E. Love[b]*

[a] Department of Chemistry, William and Mary, Williamsburg, VA, 23187, U.S.A. Email: rdpike@wm.edu

[b] Department of Chemistry, East Carolina University, Greenville, NC, 27858, U.S.A. Email: loveb@ecu.edu

Abstract – A protocol is reported which allows preparation of electron-rich benzimidazole derivatives in good yield. The reaction proceeds directly from dinitrobenzene derivatives without need of isolation of air-sensitive diamines.

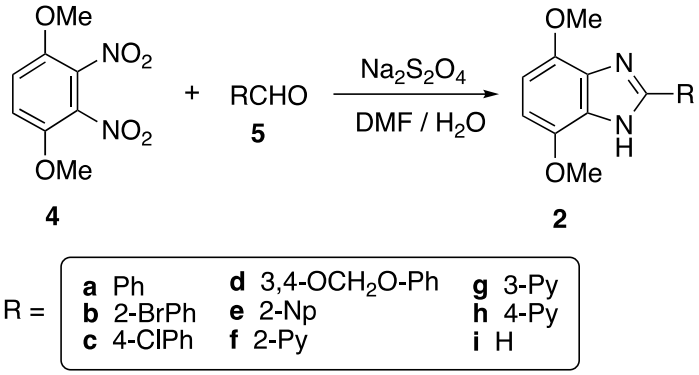
Benzimidazole-4,7-diones (**3**) are compounds of interest due to their potential use as anticancer and antifungal agents.[1-8] They are typically prepared by oxidation of the corresponding 4,7-dimethoxybenzimidazoles (**2**), which in turn are prepared from 3,6-dimethoxybenzene-1,2-diamine (**1**) (Scheme 1). Both aldehydes[1,2,7,8] and carboxylic acids[7,9,10] have been used for this reaction, with the former requiring oxidation of one of the intermediates, which is often accomplished simply by exposure to air.



Scheme 1. Synthesis of benzimidazole-4,7-diones

As part of another project, we were interested in preparing benzimidazole derivatives **2** by a simple and convenient method. Previous reports describing the synthesis of 3,6-dimethoxybenzene-1,2-diamine **1** have noted its significant air sensitivity,[9,10] which makes working with the compound somewhat problematic. We therefore desired a route to benzimidazoles **2** that would not necessitate isolation of **1**. The route that ultimately proved most successful is shown in Scheme 2, in which

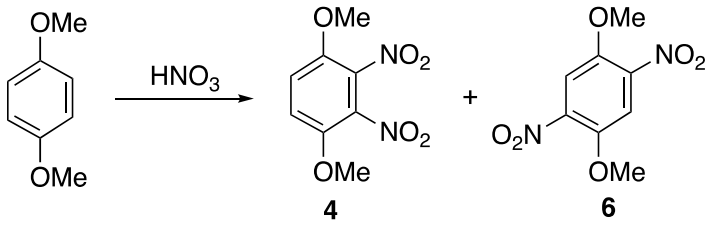
1,4-dimethoxy-2,3-dinitrobenzene (**4**) is allowed to react with aldehydes (**5**) in the presence of sodium dithionite.



Scheme 2. Synthesis of 4,7-dimethoxybenzimidazoles

Reduction of *o*-nitroaniline derivatives with sodium dithionite in the presence of aldehydes to give benzimidazoles has been reported by Yang, Fokas and coworkers.[11] More recently, Corma, Sorribes, and coworkers have described the synthesis of benzimidazoles by reaction of *o*-dinitrobenzene derivatives with aldehydes under catalytic hydrogenation conditions.[12] One example of treatment of an *o*-dinitrobenzene derivative with sodium dithionite in the presence of an aldehyde to yield a benzimidazole has been reported by Queffelec, Pellegrin and coworkers,[13] but required 10 days of heating the reaction mixture at reflux. Use of sodium dithionite in other reductive cyclizations has also been reported. For example, López and coworkers have used it to produce quinazolin-4(3*H*)-ones from *o*-nitrobenzamide derivatives.[14]

1,4-Dimethoxy-2,3-dinitrobenzene **4** was obtained along with the isomeric 1,4-dimethoxy-2,5-dinitrobenzene (**6**) by treatment of 1,4-dimethoxybenzene with concentrated nitric acid (Scheme 3).[9] As only **4** could cyclize to produce a benzimidazole, it was found that mixtures of the two isomers could be used as starting materials, and still would provide product in a high state of purity without need for chromatography.



Scheme 3. Nitration of 1,4-dimethoxybenzene

A 6:1 mixture of **4**:**6** was allowed to react with benzaldehyde in the presence of sodium dithionite to give benzimidazole (**2a**) (R = Ph). Results are summarized in Table 1.

Table 1. Investigation of Reaction Conditions[a]

Entry	Solvent	Temp. (°C)	Yield of **2a** (%)[b]
1	EtOH	reflux	11[c]
2	EtOH:H_2O (1:1)	75	34
3	EtOH:H_2O (10:1)	reflux	55
4	DME	75	0[d]
5	MeCN	reflux	0[d]
6	DMF:H_2O (10:1)	95	72
7	DMF:H_2O (10:1)	95	79[e]

[a)] Reaction conditions: 1 eq. PhCHO combined with 1.2 eq. **4**/**6** and 8.5 eq. $Na_2S_2O_4$ then heated for 3 h [b)] Yield based on total amount of **4**/**6** used, not estimated amount of **4** present. [c)] Estimated yield (product contaminated with a significant amount of **4**) [d)] Only **4** obtained. [e)] Reaction flask stoppered

Use of aqueous ethanol mixtures produced **2a** in low to moderate yields, while use of organic solvents without any added water failed to produce any of the desired product, returning starting material instead (entries 4 and 5). Product yield was increased by using conditions similar to those employed by López and coworkers, and was improved slightly when the reaction flask was stoppered as opposed to being left open to the air (entries 6 and 7).

Although use of acetonitrile as solvent failed to produce any **2a**, the starting material that was returned was found to consist entirely of the 2,3-dinitro isomer **4**, whereas the original starting material for the reaction had been contaminated with approximately 15% of the 2,5-dinitro isomer **6**. (Presumably the less hindered **6** reacted more quickly with the $Na_2S_2O_4$). The chemical literature indicates that multiple recrystallizations are often needed to obtain pure **4** from a mixture of **4** and **6**, so the use of sodium dithionite as a purification agent was briefly investigated. While simply heating mixtures of **4** and **6** with sodium dithionite in acetonitrile returned sample enriched in **4**, it was found that inclusion of an aromatic aldehyde in the mixture allows **4** to be obtained uncontaminated by **6**, often in high recovery yield. Salicylaldehyde was explored for such use, as any unreacted aldehyde (and perhaps imines derived from it) can be removed from the initial product mixture with aqueous base. For example, heating a 4.5:1 mixture of **4**:**6** with $Na_2S_2O_4$ (four equivalents based on the estimated amount of **6**) and salicylaldehyde (1.1 equivalents based on the estimated amount of **6**) in acetonitrile for 1.5 hours allowed recovery of **4** in nearly pure form in 95% yield based on the estimated amount of **4** present in the original sample (see Supplemental Information for copies of ^{1}H NMR spectra of the starting material and product of such a purification).

Optimization of reaction stoichiometry for the synthesis of benzimidazole **2a** was then conducted using purified **4** and benzaldehyde in 10:1 DMF:H_2O, the results of which are summarized in Table 2.

Table 2. Optimization of Reaction Stoichiometry

Entry	Equiv. **4**	Equiv. PhCHO	Equiv. $Na_2S_2O_4$	Yield of **2a** (%)
1	1	1.1	7	84
2	1.1	1	7.7	79
3	**1**	**1.1**	**6**	**88**
4	1	1.1	5	78
5	1	1.1	4	69

Reactions utilizing slight excesses of **4** and benzaldehyde were found to produce **2a** in similar yields (entries 1 and 2). Reduction of the amount of sodium dithionite used from seven equivalents (based on **4**) to six equivalents was found to have little effect on the yield, while use of only five equivalents resulted in slightly lower yield. Use of only four equivalents further reduced the yield, therefore use of six equivalents became part of our standard procedure. Application of the method to produce a series of known[2,7,8,15] benzimidazole derivatives was then investigated. The general procedure described in the experimental section was followed, and results are summarized in Table 3.

Table 3. Isolated Yields of **2**

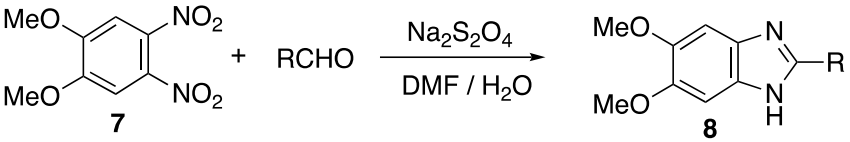
Product	R	Yield (%)
2a	Ph	88
2b	2-BrPh	67
2c	4-ClPh	81
2d	3,4-OCH_2OPh	88
2e	2-Np	67
2f	2-Py	91
2g	3-Py	68
2h	4-Py	64

Products obtained by this method were sometimes contaminated by inorganic salts or by trace amounts of DMF. Purified products could be obtained either by washing ethyl acetate solutions of the crude product with water or by suspending crude solid products in hot ethyl acetate and removing the undissolved solids by filtration. Although ^{1}H NMR spectra for the compounds obtained were consistent with those reported in the literature, the ^{13}C NMR spectra of such compounds often displayed fewer peaks than anticipated, even when taking into account free rotation around the bond to the C-2 aryl substituent and rapid tautomerization of the benzimidazole. We therefore sought further proof of structure for at

least one representative compound. Evaporation of solvent from a dichloromethane solution of pyridyl-substituted benzimidazole (**2f**) produced a collection of crystals from which structural information was obtained by means of X-ray crystallography, verifying the structure of this compound (see Supporting Information). It was later determined that obtaining ^{13}C NMR spectra in pure CD_3OD or mixtures of CD_3OD and DMSO-d_6 allowed the expected number of peaks to be observed in all but one case.[16]

Use of this method to prepare benzimidazole (**2i**) (R = H), which has been prepared by heating **1** at reflux in 98% formic acid,[10] was also investigated. Simply using either paraformaldehyde or aqueous formaldehyde in place of aromatic aldehydes **5** failed to produce **2i**. Heating **4** at 95 °C in DMF:H_2O (10:1) for three hours with two equivalents of formamidine acetate and six equivalents of $Na_2S_2O_4$ allowed isolation of **2i** in 45% yield. Extending the reaction time to 18 hours and replacing DMF with formamide increased the yield to 53% yield. A 42% yield of **2i** could be obtained under similar conditions (18 h reaction time, 10:1 formamide: H_2O as solvent) even in the absence of formamidine acetate.

As observed for **1**, 4,5-dialkoxybenzene-1,2-diamine derivatives have been found to be air-sensitive.[17] We therefore briefly examined preparation of a series of known[18-21] 5,6-dimethoxybenzimidazole derivatives (**8**) by a similar method, starting from readily available[22] 1,2-dimethoxy-4,5-dinitrobenzene (**7**) (Scheme 4). The general procedure described in the experimental section was followed, and results are summarized in Table 4.



Scheme 4. Synthesis of 5,6-dimethoxybenzimidazoles

Table 4. Isolated Yields of **8**

Product	R	Yield (%)
8a	Ph	86
8b	2-BrPh	98
8c	4-OHPh	66
8d	2-Np	51

In summary, a rapid and efficient synthetic protocol has been developed which allows preparation of dimethoxybenzimidazole derivatives from readily available starting materials.

EXPERIMENTAL

Purification of 4: A 3.00 g (13.2 mmol) sample of an approximately 4.5:1 mixture of **4**:**6** was combined with 1.98 g (9.7 mmol) of 85% $Na_2S_2O_4$ and 0.33 g (2.7 mmol) of salicylaldehyde. The mixture was taken up in 25 mL MeCN, heated to reflux and held at that temperature lightly stoppered for 90 min. The mixture was cooled to room temperature and diluted with 100 mL water and 7.5 mL 1M NaOH. The mixture was subjected to suction filtration and the precipitate washed with several portions of water. The yellow solid precipitate was initially allowed to air dry, then was placed under vacuum for several hours, yielding 2.33 g of product (95% yield based on estimated amount of **4** present in initial mixture).

General procedure for the synthesis of benzimidazoles 2 and 8: 2.0 mmol of dimethoxydinitrobenzene **4** or **7** was combined with 2.2 mmol of an aromatic aldehyde and 12.0 mmol of sodium dithionite. The mixture was taken up in 5 mL of DMF and diluted with 0.5 mL of water, then heated at 95 – 100 °C for 3 h lightly stoppered. The reaction mixture was allowed to cool to room temperature and diluted with 25 mL of water and 25 mL of saturated sodium bicarbonate solution. The precipitate was collected by suction filtration and washed several times with water. The solid was initially air-dried, then dried further under vacuum. NMR spectra of products were consistent with those reported in the literature (superscripts after compound numbers refer to references that provide spectral data).

Compound Characterization Data:

2a[12] ^{1}H NMR ($CDCl_3$): δ 8.11 (dd, *J* = 8.0, 1.8 Hz, 2H), 7.5-7.2 (m, 3H), 6.57 (s, 2H), 3.93 (s, 6H). ^{13}C NMR (CD_3OD and DMSO-d_6): δ 149.2, 141.7, 130.4, 128.4, 127.3, 126.8, 126.7, 103.5, 54.8.

2b[15] ^{1}H NMR ($CDCl_3$): δ 8.42 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.5-7.4 (m, 1H), 7.3-7.2 (m, 1H), 6.60 (s, 2H), 3.97 (s, 6H). ^{13}C NMR (CD_3OD and DMSO-d_6): δ 149.6, 143.2, 133.4, 132.5, 132.2, 131.8, 130.0, 127.9, 122.4, 103.4, 55.8.

2c ^{1}H NMR (DMSO-d_6): δ 8.27 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 6.62 (s, 2H), 3.90 (s, 6H). ^{13}C NMR (CD_3OD and DMSO-d_6): δ 149.3, 143.3, 134.9, 130.9, 129.2, 129.0, 128.7, 103.4, 55.8.

2d ^{1}H NMR ($CDCl_3$): δ 7.64 (d, *J* = 1.7 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.57 (s, 2H), 6.03 (s, 2H), 3.96 (S, 6H). ^{13}C NMR (CD_3OD and DMSO-d_6): δ 150.0, 149.3, 148.2, 142.9, 130.0, 123.5, 121.9, 108.8, 107.2, 103.3, 101.9, 55.7.

2e[7] ^{1}H NMR ($CDCl_3$): δ 8.58 (s, 1H), 8.23 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.8-7.7 (m, 2H), 7.5-7.4 (m, 2H), 6.56 (s, 2H), 3.93 (s, 6H). ^{13}C NMR (CD_3OD and DMSO-d_6): δ 150.3, 143.2, 133.9, 133.2, 130.6, 128.7, 128.6, 128.0, 127.4, 127.2, 127.0, 126.7, 124.4, 103.4, 55.7.

2f ^{1}H NMR ($CDCl_3$): δ 8.60 (d, *J* = 4.8 Hz, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 7.9-7.8 (m, 1H), 7.4-7.3 (m, 1H), 6.57 (s, 2H), 3.93 (s, 6H). ^{13}C NMR (CD_3OD): δ 149.7, 149.2, 148.1, 143.4, 137.0, 130.4, 124.2, 121.4, 102.8, 54.9.

2g[2] ^{1}H NMR (DMSO-d_6): δ 13.3 (br s, 1H), 9.42 (d, *J* = 1.7 Hz, 1H), 8.67 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.6-8.5 (m, 1H), 7.57 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.71 (br s, 1H), 6.64 (br s, 1H), 3.94 (s, 6H). ^{13}C NMR (CD_3OD): δ 150.1, 147.9, 147.8, 134.6, 126.6, 124.1, 103.1, 55.4.

2h[2] ^{1}H NMR (DMSO-d_6): δ 8.83 (d, *J* = 6.3 Hz, 2H), 8.35 (d, *J* = 6.4 Hz, 2H), 6.74 (s, 2H), 3.96 (s, 6H). ^{13}C NMR (CD_3OD and DMSO-d_6): δ 148.0, 146.7, 143.3, 139.5, 131.0, 121.5, 103.7, 55.4.

2i ^{1}H NMR ($CDCl_3$): δ 7.96 (s, 1H), 6.60 (s, 2H), 3.96 (s, 6H). ^{13}C NMR (CD_3OD and DMSO-d_6): δ 142.6, 139.2, 128.7, 102.0, 54.6.

4 ^{1}H NMR ($CDCl_3$): δ 7.21 (s, 2H), 3.93 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 145.2, 134.0, 117.4, 57.6.

8a ^{1}H NMR (DMSO-d_6): δ 8.11 (d, *J* = 8.2 Hz, 2H), 7.7-7.5 (m, 3H), 7.18 (s, 2H), 3.85 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 148.8, 148.2, 130.9, 130.5, 129.7, 128.1, 126.9, 97.6, 56.5.

8b ^{1}H NMR (DMSO-d_6): δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.6-7.4 (m, 2H), 7.17 (s, 2H), 3.82 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 148.6, 147.6, 133.9, 132.7, 132.1, 132.0, 131.8, 128.3, 121.9, 98.3, 56.4.

8c ^{1}H NMR (DMSO-d_6): δ 7.96 (d, *J* = 8.7 Hz, 2H), 7.16 (s, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 160.3, 149.4, 147.7, 130.2, 128.7, 118.8, 116.4, 97.6, 56.4.

8d ^{1}H NMR (DMSO-d_6): δ 8.69 (s, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 8.1-8.0 (m, 2H), 7.7-7.6 (m, 2H), 7.22 (s, 2H), 3.87 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 126.7, 124.9, 123.8, 97.4, 56.5.

Deposition number CCDC-2192584 for compound **2f**. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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