AN IMPROVED METHODOLOGY FOR THE PREPARATION OF 4,7-DIMETHOXY-*1H*-BENZIMIDAZOLE, A KEY INTERMEDIATE IN THE SYNTHESIS OF 1-ALKYL-*1H*-BENZIMIDAZOLE-4,7-DIONES

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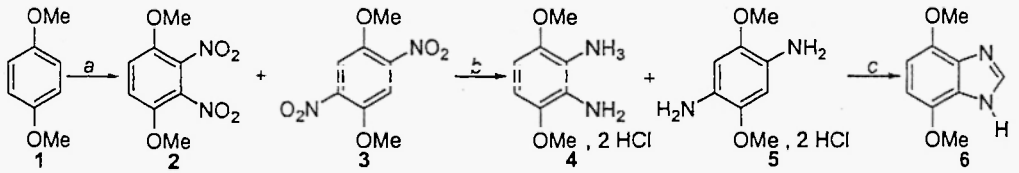
Abstract: We reported an optimized process for the preparation of key intermediate, 4,7-dimethoxy-*1H*-benzimidazole, from commercially available 1,4-dimethoxybenzene (Overall yield 52%). We successfully applied this methodology to an improved synthesis of 1-benzyl-*1H*-benzimidazole-4,7-dione (Overall yield 32% from 1,4-dimethoxybenzene).

Introduction

Benzimidazole-4,7-diones have been extensively investigated for their biological activities (1-4). In the course of our search for active compounds against the protozoan *Toxoplasma gondii*, we previously developed a route to some of these heterocyclic quinines (5,6) as inhibitors of purine nucleoside phosphorylase, an enzyme of purine salvage pathway. Our synthetic approach required large amounts of 4,7-dimethoxy-*1H*-benzimidazole **6**. However, the first attempts to its synthesis (Scheme-1), following published procedure referred to a Day's method (7), led us to a disappointing overall yield (23% calculated from commercially available 1,4-dimethoxybenzene **1**) (5). Thus, we looked for a new methodology in order to improve the access to this important synthetic intermediate.



a: HNO_3 70%, 1.5 eq, Ac_2O, 0°C, 95% yield (**2**+**3**, 45:55); *b*: Sn 5.9 eq, HCl 37%, 98% yield (**4**+**5**); *c*: HCOOH, Δ, 25 % yield

Scheme-1

Results and Discussion

Among the modern reported methods for nitration of **1** (table I), we chose the classical reagent HNO_3 as it is simple to use in a large scale reaction. We then explored different reaction conditions in order to improve the yield in regioisomer **2** and to facilitate the purification process. With HNO_3 (2 eq) in acetic anhydride at 0°C, we obtained a good yield in the mixture of compounds **2** and **3** (95%), but with a marginal selectivity in favour of the undesirable regioisomer **3** (45/55). On the other hand, the application of method E led to a similar yield (97%) but with a greater regioselectivity (90/10). Moreover, we developed a large scale chromatographic procedure allowing preparation of pure **2** in 87% yield and great quantity (see experimental section).

Table-1: Comparative methods for nitration of 1,4-dimethoxybenzene 1

method	experimental conditions	ratio **2**/**3**	yield (%)
A	HNO_3 (5.6 eq), AcOH, 90°C	not reported	80 (8)
B	HNO_3 (1.5 eq), Ac_2O, 0°C	not reported	70 (9)
C	NO_2, O_3, CH_2Cl_2, 0°C	54/46	81 (10)
D	NO_2BF_3 (2 eq), DME, -50°C	100/0	76 (11)
E	HNO_3 70% (19 eq.), 0°C then 90°C	90/10	89 (12) (pure **2**)

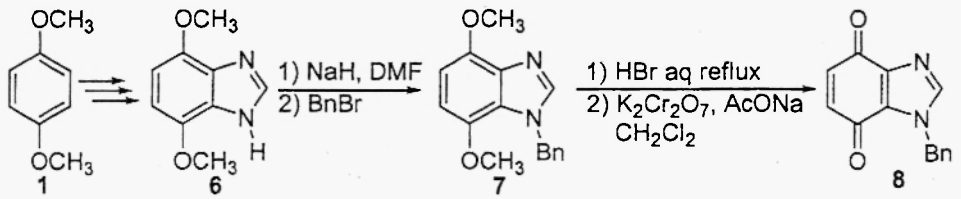
Several experimental conditions were reported in order to reduce compounds **2** and **3** (Table-2). The reported yields were rather low, and we undertook a study to find better reaction conditions. In our hands, attempts to use Fe in water(13) or in acidic medium (HCl 12N) failed. In the case of 2,3-dinitro-1,4-dimethoxybenzene **2** as that of further substituted derivatives (4), Sn/HCl proved to be the best reagent. After several trials, conducted in order to minimise amount of Sn, we found that the best experimental conditions corresponded to the use of 5,8 eq Sn in HCl 12N at 100°C. Thus, we obtained the mixture of compounds **4** and **5** in almost quantitative yield (98%), and the synthesis of **6** was achieved, without further purification, *via* a Phillips (14) cyclisation process.

Table-2 : Comparative methods for reduction of 2 and 3

method	substrate(s) (**2**/**3**)	experimental conditions	yield (%)
F	**2**	1) H_2, PtO_2, EtOH; 2) HCl (12N)	40 (7)
G	**2**	1) H_2, Ni Raney, EtOH, 50°C ; 2) HCl (12N)	60 (15)
H	**2**	Sn (14,6 eq), HCl (12N), 100°C	not reported (10)
I	**2** + **3** (36/64)	$Na_2S_2O_4$ (10 eq), THF/MeOH (1/1), reflux	44 (8)

The overall yield of **6** from dinitro derivative **2** was 60%. It is noteworthy that a 47 % overall yield was obtained from a 90/10 mixture of **2** and **3** (calculated from **2** only) whereas this yield drastically decreased from the 45/55 mixture (25%). This lower yield seems most likely due to the final sensitive chromatographic purification of **6**, a recrystallization being possible only in the case of an enriched mixture in compound **2**. Finally, the yield of 4,7-dimethoxybenzimidazole **6** from dimethoxybenzene **1** was increased from 23% to 52 %, with a simplified process.

Alkylation of compound **6** led to various derivatives, easily oxidized by improved procedures to give benzimidazolequinones. Thus, access to 1-benzylbenzimidazole-4,7-dione **8** was described (5) *via* the reduction of a mixture of dinitro compounds **2** and **3** (45/55) in a 11% overall yield from compound **1** (scheme 2). When the synthesis of **8** was carried out from pure **2** without any purification steps of intermediates, an overall yield of 37% from **2** was obtained.



Scheme 2

Conclusions

We describe an optimized process for the synthesis of 4,7-dimethoxy-1*H*-benzimidazole **6**, which is a key intermediate in the synthesis of various benzimidazole-4,7-dione derivatives with potential biological activities. Thus, dimethoxybenzimidazole **6** and benzimidazolequinone **8** were isolated respectively in 52% and 32 % overall yield from commercial dimethoxybenzene **1**, whereas the best reported yields to **6** and to **8** were respectively 23 % (5) and 11% (6).

Experimental Section

General

1,4-Dimethoxybenzene **1** was obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ using a Bruker 300 MHz. The chemical shift data are reported as δ (ppm) downfield from tetramethylsilane, which was used as an internal standard.

Preparation of 1,4-dimethoxy-2,3-dinitrobenzene (2).
Compound **2** was prepared according to the procedure described in the literature (12), scaled to 15 g (108.70 mmol) of **1**; yield 24.04 g (97%; **2/3** : 90/10). Purification of **2** was carried out by chromatography (8 g of a mixture of **2** and **3**: 15 cm Ø column, 1 kg of silica, AcOEt/petroleum ether 50:50 as eluent). Purified products were obtained in quantitative yield. The same silica gel can be used for 3 successive scans.

Preparation of 4,7-dimethoxy-1*H*-benzimidazole (6).
A mixture of **2** (10.15 g, 44.52 mmol), tin granular (31 g, 262 mmol), and concentrated HCl (320 mL) was heated up to 100°C with stirring. After 3h, the mixture was cooled to 0°C. The solution was filtered under vacuum and the white precipitate dried. The latter was added to formic acid (93 mL) and the mixture was heated to reflux for 5.5 h. After cooling to r. t., the solution was evaporated to dryness. The residue was dissolved in warm water (50 mL) and aqueous ammonia solution (20%) was added until pH 9. The precipitate was filtered under vacuum, washed with water and dried. Recrystallization from chloroform led to pure **6**; yield 4.75 g (60%).

Preparation of 1-benzyl -1*H*-benzimidazole-4,7-dione (8).
A solution of crude 4,7-dimethoxy-1*H*-benzimidazole **6** (1.25 g), obtained by following the above procedure, in dry DMF (100 mL), was added dropwise, over 15 min, to a suspension of NaH (60% in mineral oil; 0.298 g, 7.43 mmol) in the same solvent (9 mL). The reaction mixture was stirred for 15 min and benzyl bromide (1.12 g, 6.56 mmol) was rapidly added. After stirring for 12 h, DMF was removed under vacuum. The residue was then dissolved in CH_2Cl_2 (180 mL). The solution was filtered, washed with a saturated K_2CO_3 solution (3 x 270 mL) and dried over Na_2SO_4. Evaporation of the solvent led to crude 1-benzyl-4,7-dimethoxy-1*H*-benzimidazole **7** (1.12 g), which was added to aqueous 48% HBr (30 mL) and heated to reflux for 4h. After cooling to 4 °C over 12h, the precipitate was filtered off and dissolved in water (70 mL). Then, an aqueous solution of 6.7 N HCl (3 mL), an aqueous solution of 0.3 M $K_2Cr_2O_7$ (6 mL), sodium acetate (2.10 g, 25.56 mmol) and CH_2Cl_2 (130 mL) were successively added. Stirring was maintained 30 min at r. t. The organic layer was separated, washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography (AcOEt/petroleum ether; 67/33); yield 0.44g (37% from **2**).

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