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Selective phenol alkylation for an improved synthesis of 2-arylbenzimidazole H_4 receptor ligands

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ABSTRACT

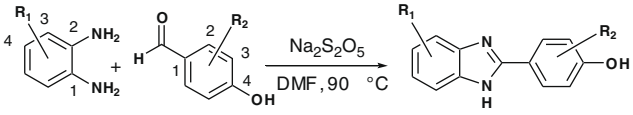
Alkylation of a phenol OH in the presence of a free benzimidazole NH was investigated and found to be highly dependent on the substitution of the benzimidazole and phenol rings. The modification of our original synthesis of 2-arylbenzimidazole H_4 receptor ligands has resulted in improved yields and ease of isolation of final products.

1. Introduction

During the development of our H_4 receptor modulator program, we were interested in synthesizing larger quantities of previously reported 2-arylbenzimidazole derivatives.[1] Our previous synthesis allowed for rapid introduction of various points of diversity on the 2-aryl benzimidazole core via a late stage benzimidazole formation. However, upon scaling up the reactions, we encountered problems both with the reproducibility of the late stage benzimidazole condensation and with the isolation of desired products. Modification of the synthesis to incorporate the benzimidazole formation earlier in the sequence resulted in very clean reactions when performed on variously substituted benzaldehyde phenols (Table 1). The condensation reactions were rapid under an atmosphere of air and product isolation was readily accomplished by pouring the reactions into water and filtering the resulting solid. The products were generally isolated in greater than 90% yield and in greater than 90% purity.

With ready access to benzimidazole phenol intermediates, we approached the task of selectively alkylating the phenol OH in the presence of the benzimidazole NH, of which there is limited precedence.[2,3] Not only do benzimidazole and phenol have similar pK_as, but the relative order of acidity switches depending on the solvent: benzimidazole (pK_a = 16.4 in DMSO,[4] 12–13 in H_2O[5]) and phenol (pK_a = 18.0 in DMSO;[4] 10.0 in H_2O[4]). This suggested that a selective alkylation of the phenol could be achieved with appropriate choice of solvent. Starting with conditions that we had used for the alkylation of benzaldehyde phenols,[1] K_2CO_3 in acetonitrile, the desired mono-alkylated phenol was isolated as the desired product (50% yield) along with bis-alkylation products and minor amounts of dimeric products. We thus initiated a scan of various solvents and bases to improve the selectivity of the phenol alkylation. The results in Table 2 demonstrated that on our test substrate, 2-(4-hydroxyphenyl)-5-methyl benzimidazole, there was a significant effect of the choice of base and solvent on the course of these reactions. Acetonitrile or acetone as solvent combined with Cs_2CO_3 as base proved to be the best combination for selective alkylation of the phenol (entries 2 and 7). It is interesting to note that with DMF as the solvent the reaction did not go to completion after 24 h at 70 °C with Cs_2CO_3 as base, but the reaction was complete with K_2CO_3 (entries 4 and 5). In addition, the DMF reactions showed significantly more by-products than acetonitrile or acetone.[6] Other solvents scanned were likewise inferior to acetonitrile and acetone either giving very slow reaction or showing significant by-product formation. Although acetone was more selective for the mono- over bis-alkylated product, the reaction rate was too slow to be practical, and acetonitrile was used in

Table 1
Formation of benzimidazole phenols



Entry	R1	R2	Yield (%)	Purity (%)
1	3-CH_3	–H	93	91
2	4-CH_3	–H	>99	96
3	4-CH_3	3-OMe	92	95
4	4-CH_3	3-Cl	>99	90
5	4-CH_3	2-OMe	>99	85
6	4-Cl	–H	>95	>98
7	4-Cl	2-Cl	>95	92
8	4-Cl	3-Cl	95	90
9	4-Cl	2-OMe	98	90
10	4-OCH_3	–H	85	>98
11	4-F, 3-Me	–H	85	97

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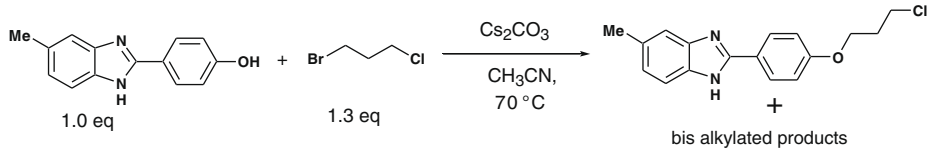
Table 2
Optimization of alkylation of 2-(4-hydroxyphenyl)-5-methyl benzimidazole



Entry	Solvent	Base	% Conversion[a]		Ratio	Yield[a] (%)
			@ 30 min (%)	@ 24 h (%)	*O*-Alkyl:bis-alkyl[a]	
1	CH_3CN	K_2CO_3	2	83 (n = 3)	3.3:1	50
2	CH_3CN	Cs_2CO_3	30	97 (n = 2)	6.0:1	70
3	CH_3CN	DBU	50	n/a	Complex mixture	
4	DMF	K_2CO_3	10	>99	Complex mixture	
5	DMF	Cs_2CO_3	0	30	Complex mixture	
6	DMF	DBU	46	48	Complex mixture	
7	Acetone[c]	Cs_2CO_3	15	71	16:1	
8	DMSO	Cs_2CO_3	38	94	Complex mixture	
9	NMP	Cs_2CO_3	30	78	Complex mixture	
10	Dioxane	Cs_2CO_3	0	68	Complex mixture	
11[b]	CH_3CN	Cs_2CO_3	30	>99	5.5:1	81

[a] Unless otherwise noted, results based on single experiment (n = 1).
[b] 1.1 equiv of bromochloropropane used.
[c] Temperature = 56 °C boiling point of acetone.

subsequent reactions. Finally lowering the amount of bromochloropropane from 1.3 to 1.1 equiv (entry 11) resulted in a similar selectivity, but in a higher overall yield of the mono-O-alkylated product.

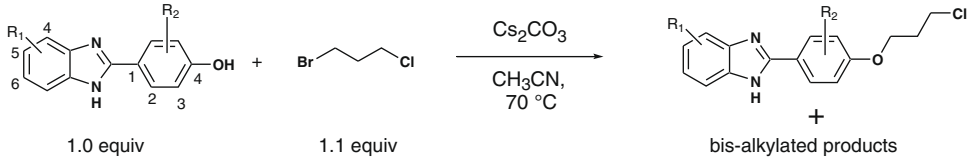
With conditions favoring the mono O-alkylation of our test substrate, we investigated the selectivity of this reaction as a function of the electronic and steric environment around the phenol and the benzimidazole. As seen in Table 3, phenol alkylation was favored by the presence of a methyl group at the 4-position of the benzimidazole (compare entries 1–3), though sterics may play a role in favoring the phenol over the benzimidazole, the bis-alkylated product in this case was a 1:1 mixture of *N*-1 and *N*-3 regioisomers. By comparing entry 1 with entries 3–5 it is clear that the presence of an electron-withdrawing group (EWG) such as chlorine on the benzimidazole diminishes the preference for O-alkylated products.

A mild electron-donating group (EDG) such as 5-methyl (entry 3) is equivalent to a 5-H when comparing the ratio of mono- versus bis-alkylation products; however, 5-methyl substitution results in higher isolated yield of *O*-alkyl product. The 5-OMe (entry 4) group can act as either an EWG or an EDG depending on whether it is *meta* or *para* to the reacting center.[7] In the case of these alkylation studies, it appears that the OMe group behaves more like an EWG than like an EDG on the benzimidazole nucleus.

The addition of substituents around the phenolic ring also had a marked effect on the alkylation selectivity. The parent 5-chloro benzimidazole with no substitution on the phenolic aryl ring (entry 5) showed a low 1.4:1 selectivity. Both 2-Cl and 3-Cl substitutions on the central aromatic ring (entries 6 and 7) increased the amount of the alkylation at the phenol. Interestingly, the 2-OMe and 3-OMe substitution (entries 8 and 9) had similar effects on the degree of phenol alkylation as the chloro substitution. The combination of 5-Me substituent on the benzimidazole and a 3-Cl on the phenol (entry 10) gave very good selectivity for the desired phenol alkylation product (16:1). And in the case of the final entry 11 the presence of 2 methyl groups near the benzimidazole N–H favors the alkylation of the phenol even though the electron-withdrawing 5-F substituent on the benzimidazole would be predicted to increase N-alkylation.

To complete the synthesis of desired H_4 ligands, the O-alkylated product was treated with *N*-methyl piperazine in the presence of

Table 3
Scope and limitation of alkylation



Entry	R1	R2	% Conversion	Yield (*O*-alkyl) (%)	Ratio *O*-Alkyl:bis-alkyl
1	H	H	85	48	5:1
2	4-Me	H	95	66	11:1
3	5-Me	H	90	81	5:1
4	5-OCH_3	H	71	62	3.4:1
5	5-Cl	H	83	54	1.4:1
6	5-Cl	2-Cl	95	67	3.0:1
7	5-Cl	3-Cl	57	36	2.0:1
8	5-Cl	3-OCH_3	82	52	2.3:1
9	5-Cl	2-OCH_3	84	71[a]	4:1
10	5-Me	3-Cl	82	78	16:1
11	4-Me, 5-F	3-Me	95	74	9:1

[a] Yield of mixture of mono- and bis-alkylated products.

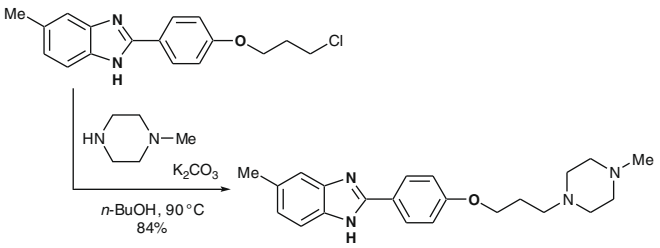


Figure 1. Nucleophilic displacement of chloroalkane.

NaI in *n*-BuOH at 90 °C to afford the desired alkylated diamine product in 84% yield. The overall yield for this sequence starting from the phenol aldehyde is 67% (Fig. 1).

These results indicate that in the case of alkylation, the phenol and benzimidazole are very similar in reactivity and that phenol alkylation is preferred when the steric environment around the benzimidazole is increased. Additionally, it appears that an EWG on the benzimidazole favors N-alkylation while the electronic effects of phenol substitution are not easy to predict.

2. Experimental

2.1. Representative benzimidazole condensation procedure: 2-(4-hydroxyphenyl)-5-methyl benzimidazole

A solution of the 4-methyl-1,2-phenylenediamine (5.8 g, 47 mmol) and 4-hydroxybenzaldehyde (5.5 g, 45 mmol) in DMF (90 ml) was treated with $Na_2S_2O_5$ (8.9 g, 45 mmol) and the reaction mixture heated to 90 °C for 2 h. The reaction mixture was cooled to rt and then diluted up to 600 ml with ice/water. The resulting suspension was stirred for 4 h then cooled to 0 °C and filtered through a glass fritted funnel, washed with cold water and the solid was dried under vacuum to yield 10.0 g (99% yield) of 2-(4-hydroxyphenyl)-5-methyl benzimidazole which was 97% pure by HPLC.

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.82 (br s, 1H), 10.75 (s, 1H), 8.15 (d, J = 8.8, 2H), 7.69 (d, J = 8.3, 1H), 7.59 (s, 1H), 7.37 (d, J = 8.5, 1H), 7.11 (d, J = 8.8, 2H), 2.54 (s, 3H).

2.2. Representative alkylation procedure: 2-[4-(3-chloro-propoxy)-phenyl]-5-methyl-1*H*-benzimidazole

A suspension of 2-(4-hydroxyphenyl)-5-methyl benzimidazole (224 mg, 1.0 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol) in acetonitrile (3 ml) was treated with 1-bromo-3-chloro propane (0.1 ml, 1.1 mmol) and the reaction mixture heated to 70 °C for 16 h. The reaction mixture was cooled to rt and then diluted with chloroform (15 ml) and filtered through a glass fritted funnel to remove inorganic solids. The filtrate was concentrated under reduced pressure and the crude residue was purified on 12 g SiO_2 eluting with 0–50% ethyl acetate/hexanes to provide the 2-[4-(3-chloro-propoxy)-phenyl]-5-methyl-1*H*-benzimidazole (243 mg, 81% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42–8.31 (m, 2H), 7.73 (d, J = 8.1, 1H), 7.63 (s, 1H), 7.46–7.36 (m, 2H), 7.34–7.23 (m, 1H), 4.47 (t, J = 6.0, 2H), 4.11 (t, J = 6.5, 2H), 2.80 (dt, J = 3.6, 1.8, 2H), 2.71 (s, 3H).

2.3. Representative chloride displacement: 5-methyl-2-{4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-1*H*-benzoimidazole

2-[4-(3-Chloro-propoxy)-phenyl]-5-methyl-1*H*-benzimidazole (300 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol), NaI (150 mg, 1 mmol), and *N*-methyl piperazine (0.33 ml, 3.0 mmol) in *n*-butanol (4 ml) were heated to 90 °C for 22 h. The reaction mixture was cooled to rt and then diluted with chloroform and filtered through a glass fritted funnel to remove inorganic solids. The filtrate was concentrated under reduced pressure and the crude residue was purified on 12 g SiO_2 eluting with 0–10% 2 M NH_3OH in $MeOH/CH_2Cl_2$ to provide the 5-methyl-2-{4-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-1*H*-benzoimidazole (306 mg, 84% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, J = 8.8, 2H), 7.43 (s, 1H), 7.35 (s, 1H), 7.05 (d, J = 8.9, 3H), 4.13–4.05 (m, 1H), 2.56 (d, J = 7.9, 7H), 2.45 (s, 4H), 2.29 (s, 3H), 2.08–1.91 (m, 1H).

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