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SYNTHESIS OF NEW (BENZIMIDAZOLYL)PIPERAZINES WITH AFFINITY FOR THE 5-HT$_{1A}$ RECEPTOR VIA Pd(0) AMINATION OF BROMOBENZIMIDAZOLES

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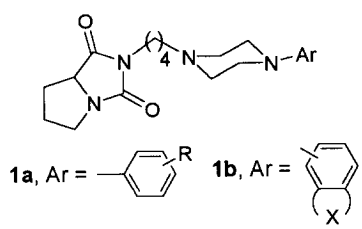
Abstract: The synthesis of a new family of (benzimidazolyl)piperazines has been developed through Pd(0) mediated amination of 4- and 6-bromobenzimidazole derivatives. Preliminary studies showed that some of these compounds are potent 5-HT$_{1A}$ receptor ligands.

The discovery of new ligands for the family of serotonin receptors is an area of active research in Medicinal Chemistry. Within this field the 5-HT$_{1A}$ receptor has been intensively studied[1] because it is involved in physiological processes and psychiatric disorders such as anxiety and depression. In addition to these therapeutic uses, serotonergic 5-HT$_{1A}$ agonists have been recently suggested to be employed as neuroprotective agents[2] and the effect of these drugs may be therapeutically relevant. For these reasons we are currently involved in the design of new active and selective agents for this receptor. In this way, we have found that arylpiperazines **1a** (Scheme 1) are potent 5-HT$_{1A}$ ligands.[3] 3D-QSAR studies[4] showed that increasing the size of the substituent of the aromatic ring could enhance the affinity for the 5-HT$_{1A}$ receptor and therefore we undertook the synthesis of arylpiperazines with bulkier aryl groups, **1b**. One of the structures that we considered had a benzimidazole ring attached to the piperazine through carbon 4 or 5 and this required an efficient entry to 1-[benzimidazol-4(7)- and -5(6)-yl]piperazines.

Scheme 1



Benzimidazole derivatives are becoming increasingly important.[5] Nevertheless, despite of their importance there are few methods available to prepare benzimidazole derivatives bearing substituents attached to the homocycle since most of the routes known are directed to functionalize carbon-2 and nitrogens (N-1, N-3).[6] On the other hand, most methods to obtain arylpiperazines involve cyclization of aromatic amines and bis(haloethyl)amines.[7] However, these procedures present some problems such as the use of toxic reagents and the difficult isolation of the products. Moreover, in our hands treatment of 4-amino-1-tritylbenzimidazole with bis(chloroethyl)amine under a number of different conditions did not yield the expected 1-(benzimidazol-4-yl)piperazine but complex crude mixtures with extensive decomposition. These disappointing results prompted us to explore alternative routes to reach our target compounds.

The metal-mediated coupling of aromatic halides and triflates with amines has become a powerful tool to synthesize aromatic amines, especially since Buchwald and Hartwig independently studied the process from a synthetic and mechanistic standpoint.[8] Because of the broad scope of the amination reaction, we considered it suitable for our purposes.[9] In this paper, we would like to report our results on the synthesis of 4(7)- and 5(6)-(benzimidazolyl)piperazines and on the synthesis of a new family of heteroarylpiperazines with activity for the 5-HT$_{1A}$ receptor.

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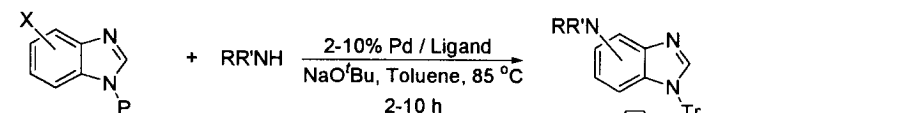
4(7)-Bromobenzimidazole **2**[10] was tritylated under standard conditions (TrCl/NaH/*n*-Bu_4NI/THF) yielding a single *anti* isomer, 4-bromo-1-tritylbenzimidazole, **3**. Treatment of **3** with morpholine (1.4 equiv) at 85 °C in the presence of $Pd_2dba_3{\cdot}CHCl_3$ (2-10%), dppp (2-10%), NaO^tBu (1.4 equiv) in toluene rendered 4-(benzimidazol-4-yl)morpholine **4a** in 65% yield. We did not observe the corresponding reduction product (1-tritylbenzimidazole, **5**)[11] in the ^1H NMR spectrum (300 MHz) of the crude reaction mixture (Scheme 2, Table 1, entry 1). Table 1 gathers our results on these couplings. Therefore, 1-methylpiperazine reacted with bromobenzimidazole **3** giving an excellent yield of **4b** when $Pd_2dba_3{\cdot}CHCl_3$ or $Pd(OAc)_2$ were used as catalyst along with dppp. However, when these conditions were applied to unprotected **2** no coupling product could be detected (Table 1, entries 2-4).

The behavior of **3** with an excess of piperazine (4 equiv) was also examined, and the corresponding (benzimidazolyl)piperazine **4c** was produced under slightly different conditions. The use of $Pd_2dba_3{\cdot}CHCl_3$/dppp did not yield the expected product but a mixture of starting material **3** and reduction product **5** (75:25) after 24 h of reaction, probably because of a competitive β-elimination process. Changing the catalyst system to $Pd(OAc)_2$/dppp gave a small amount of **4c** in the crude mixture (25:50:25, **3**:**4c**:**5**). However, the best result was obtained with $Pd_2dba_3{\cdot}CHCl_3$/BINAP obtaining **4c** with 87% yield (Table 1, entries 5-7). The corresponding dimer was not produced under these conditions; even in the presence of an excess of **3** and after prolonged reaction times (48 h), we only observed traces of a compound that was tentatively assigned as dimer along with **4c** by ^1H NMR. Other amines submitted to the coupling reaction showed a lower reactivity.[12] Thus, hexylamine (Table 1, entry 8) led to only 28% conversion after 48 h. In contrast, $PhNH_2$ afforded the corresponding amine **4e** which was isolated pure in 54% yield at 60% conversion (Table 1, entry 9).

Scheme 2



2, X = 4(7)-Br, P = H
3, X = 4-Br, P = Tr
5, X = H, P = Tr
6, X = 5(6)-Br, P = H
7a, X = 5-Br, P = Tr
7b, X = 6-Br, P = Tr
8, X = 5-I, P = Tr

4a, RR'N = 4-N(O)
4b, RR'N = 4-N(NCH$_3$)
4c, RR'N = 4-N(NH)
4d, RR'N = 4-NHHex
4e, RR'N = 4-NHPh
9, RR'N = 5-N(NH)

Table 1. Pd(0) Amination of Bromobenzimidazoles

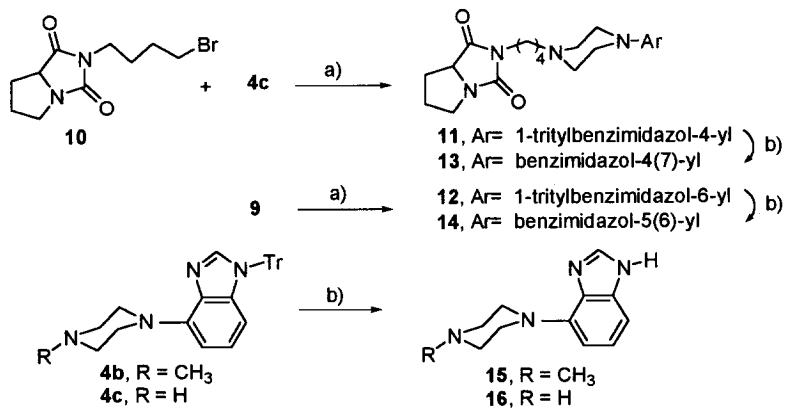
Entry	Substrate	RR'NH	Catalyst/Ligand	Product (yield%)[a]
1	**3**	morpholine	$Pd_2dba_3{\cdot}CHCl_3$/dppp	**4a** (65%)
2	**3**	1-methylpiperazine	$Pd_2dba_3{\cdot}CHCl_3$/dppp	**4b** (97%)
3	**3**	1-methylpiperazine	$Pd(OAc)_2$/dppp	**4b** (97%)
4	**2**	1-methylpiperazine	$Pd(OAc)_2$/dppp	-[b]
5	**3**	piperazine	$Pd_2dba_3{\cdot}CHCl_3$/dppp	-[c]
6	**3**	piperazine	$Pd(OAc)_2$/dppp	**4c**[d]
7	**3**	piperazine	$Pd_2dba_3{\cdot}CHCl_3$/BINAP	**4c** (87%)
8	**3**	hexylamine	$Pd_2dba_3{\cdot}CHCl_3$/BINAP	**4d**[e]
9	**3**	aniline	$Pd_2dba_3{\cdot}CHCl_3$/BINAP	**4e**[f] (54%)
10	**7a**	piperazine	$Pd_2dba_3{\cdot}CHCl_3$/BINAP	-[g]
11	**8**	1-methylpiperazine	$Pd_2dba_3{\cdot}CHCl_3$/dppp	-[g]
12	**7b**	piperazine	$Pd(OAc)_2$/BINAP	-[h]
13	**7b**	piperazine	$Pd(OAc)_2$/BINAP	**9** (60%)[i]

[a]Yield of isolated pure compounds. [b]No reaction was observed. [c]A 75:25 mixture of **3** and **5** was observed in the reaction crude (^1H NMR, 300 MHz). [d]A 25:50:25 mixture of **3**, **4c** and **5** was observed in the reaction crude (^1H NMR, 300 MHz). [e]A 72:28 mixture of **3** and **4d** was observed in the reaction crude (^1H NMR, 300 MHz). **4d** was not isolated from this mixture. [f]60% conversion after 20 h of reaction. [g]A 50:50 mixture of starting material and **5** was observed in the reaction crude (^1H NMR, 300 MHz). [h]A 30:40:30 mixture of **7b**, **5** and **9** was observed in the reaction crude (^1H NMR, 300 MHz). [i]A 15% of **5** was also obtained. Cs_2CO_3 instead of NaO^tBu was employed.

5- and 6-Bromobenzimidazoles[13] were also considered as substrates for the amination reaction. Therefore, **6** was protected as before to produce a separable 50:50 mixture of the *N*-trityl derivatives **7a** and **7b** that in principle would converge to a single benzimidazole derivative after the coupling process and deprotection. However, unexpectedly we found that these regioisomers displayed a very different reactivity. Thus, 5-bromo-1-tritylbenzimidazole **7a** was not a suitable substrate for the coupling reaction yielding starting material along with variable amounts of reduction product (**5**) under a number of conditions tried.[14] The reaction with 5-iodo-1-tritylbenzimidazole **8**[15] was also tried and again starting material and reduction product **5** were obtained (Scheme 2, Table 1, entries 10-11). On the other hand, 6-bromo-1-tritylbenzimidazole **7b** reacted more readily than its isomer **7a** (entries 12 and 13). Thus, a low conversion to the corresponding (benzimidazolyl)piperazine **9** (30%) along with important amounts of reduction product **5** (40%) were produced after treatment of the bromo derivative **7b** with an excess of piperazine, using $Pd(AcO)_2$/BINAP and NaO^tBu, however, the use of Cs_2CO_3 as base instead of NaO^tBu allowed to obtain the desired piperazine **9** along with small amounts of reduction product **5**, that could be easily purified to render pure **9** in 60% yield.

To continue with our initial project on the design of new ligands for serotonin 5-HT_{1A} receptor we addressed the synthesis of heteroarylpiperazines **1b** from the above (benzimidazolyl)piperazines **4c** and **9**. Therefore, **4c** and **9** were treated with bromoderivative (±)-**10**[3a] to yield (±)-**11** and (±)-**12**. Standard acidic conditions[16] (AcOH/H_2O/THF) allowed for the smooth removal of the protecting group on the final ligands to produce (±)-**13** and (±)-**14** in 85% and 65% yield respectively. Simple (benzimidazolyl)piperazines **4b** and **4c** were also submitted to this deprotection protocol rendering **15** and **16**[17] in good yields (Scheme 3).

Scheme 3



a) NEt_3, CH_3CN, Δ, 80% for **11**; 63% for **12**. b) AcOH, THF, H_2O, 85% for **13**, 65% for **14**, 86% for **15**, 66% for **16**.

Preliminary studies on the in vitro affinity at 5-HT_{1A} receptors were carried out for **4b**, **4c**, **13**, and **15** by radioligand binding assays, using [^{3}H]-8-OH-DPAT in rat cerebral cortex membranes.[18] Compounds **13** and **15** displayed high affinity for the 5-HT_{1A} receptor (K_i = 1.21 ± 0.02 and 4.72 ± 0.50 nM, respectively), whereas tritylated derivatives **4b** and **4c** were inactive. These results indicate that arylpiperazines **13** and **15** are new potent 5-HT_{1A} receptor ligands. Thus, the fragment 1-(benzimidazol-4-yl)piperazine represents a novel and readily accessible pharmacophoric moiety in the research for new potent and selective 5-HT_{1A} ligands.

In summary, we have synthesized a new class of (benzimidazolyl)piperazines via Pd(0) amination of bromobenzimidazole derivatives. Some of these compounds have showed to be potent 5-HT_{1A} receptor ligands. The synthesis of new analogues, assessment for 5-HT_{1A} receptor affinity and further pharmacological characterization are in progress in our laboratory and the results will be published in due course.

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