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Palladium Catalyzed Amination of 2-Chloro-1,3-Azole Derivatives: Mild Entry to Potent H_1- Antihistaminic Norastemizole

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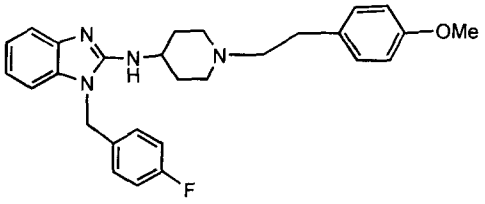
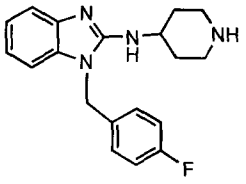
This manuscript is dedicated to the occasion of Professor Carl R. Johnson's 60th birthday

Abstract: *Palladium-catalyzed selective amination of 4-fluorobenzyl-2-chlorobenzimidazole with 4-aminopiperidine provided a simple solution for the norastemizole synthesis. Pd-catalyzed amination of other 2-chloro-1,3-Azole derivatives are exploited.* © 1997 Elsevier Science Ltd.

There has been significant medicinal interest in derivatives of 2-aminoimidazoles and related heterocycles due to their varied biological activity toward numerous diseases.[1] For example, astemizole is a potent nonsedating histamine H_1-receptor antagonist which has been introduced as a therapeutic agent in allergic diseases. Norastemizole, an extremely active metabolite of astemizole, is currently in phase II clinical trails and has the potential to be devoid of the adverse effects characteristic of astemizole.[3] These potent antihistamines contain a 2-aminoimidazole moiety, whose preparation lacks synthetic practicality. Although widely studied,[4] amination at the 2-position of 1,3-azoles has limited synthetic applicability because of harsh reaction conditions and functional group intolerance. Disclosed here in is a mild protocol for the preparation of 2-amino-1,3-azole derivatives via palladium-catalyzed amination of 2-chloro-1,3-azoles and a practical synthesis for norastemazole and its derivatives.



Astemizole



Norastemizole (1)

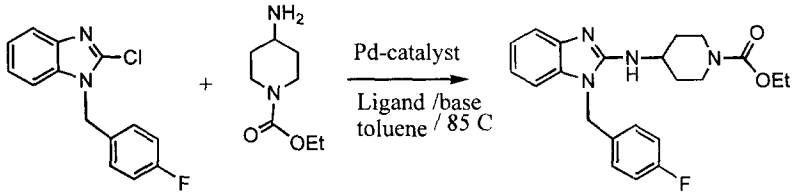
In our antihistaminic program an efficient process for Norastemizole was explored. After evaluation of several synthetic strategies, our focus centered on the coupling of readily available 4-fluorobenzyl-2-chlorobenzimidazole with ethyl 4-amino-1-piperidinecarboxylate. Unfortunately, thermal coupling of the chloroimidazole and amine required high temperatures and prolonged reaction times producing impurities and low product yields.[5]

Recently, Buchwald[6] and Hartwig[7] independently demonstrated several palladium-catalyzed amination reactions of aryl bromides. Although extrapolation to C-Cl activation appeared tenuous, Beller and co-workers have shown that aryl chlorides can be coupled with amines using a palldacycle catalyst in the presence of potassium t-butoxide at 135 °C.[8] These important discoveries led us to believe that a polarized C-Cl bond at the C-2 position of imidazoles may undergo rapid and mild amination with catalytic amounts of palladium. Indeed, when 4-fluorobenzyl-2-chlorobenzimidazole and ethyl 4-amino-1-piperidinecarboxylate were exposed to Buchwald's coupling conditions: 1.4 equiv. sodium t-butoxide in the presence of 0.25 mol % $Pd_2(dba)_3$ with 0.75 mol % of BINAP in toluene at 85 °C for 1h, an 84% isolated yield (>99.5% conversion) of the corresponding aminoimidazole **4** was obtained (Table 1, entry 3). Control experiments indicate that without the Pd-catalyst system, when 4-fluorobenzyl-2-chlorobenzaimidazole and 1-ethyl-carboxy-4-amino-piperidine were heated in toluene at 110 °C for one day, <2 % product formation was observed (entry 1). Carbamate **4** prepared from this procedure can be simply converted to the desired norastemizole by acid hydrolysis.[5]

Table 1 shows the influence of reaction temperature, catalyst system and catalyst loading on the rate of the reaction. Temperatures below 80-85 °C resulted in decreased reaction rates (entry 6), and replacement of NaOtBu with

triethylamine or 2,6-lutidine gave no reaction (entries 7 and 8). Compound **2** proved to be extremely inert to the $Pd_2(dba)_3$-DPPF catalytic system for amination by amine **3**. Hartwig's coupling conditions gave lower product yields, while requiring a longer reaction time, higher reaction temperature and greater catalyst loading (entry 9). Of the catalyst systems studied, the $Pd_2(dba)_3$ -BINAP system was optimal. Importantly, the catalytic loading could be reduced to 0.25 mol% of $Pd_2(dba)_3$ in the presence of 0.75 mol% of BINAP with minimal effects on the reaction rate and product yield (entries 2 and 3).

Table 1

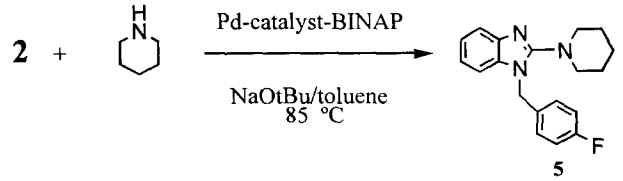


2 **3** **4**

Entry	Pd-catalyst (mol %)	Base (equv.1.4)	Ligand (mol %)	Temperature °C	Reaction h	HPLC assay yield (isolated yield %)
1	----	-----	----	85	24	<3 %
2	$Pd_2(dba)_3$ (0.5)	NaOt-Bu	BINAP (1.5)	85	0.5	>98
3	$Pd_2(dba)_3$ (0.25)	NaOt-Bu	BINAP (0.7)	85	1.0	>95 (85)
4	$Pd_2(dba)_3$ (0.125)	NaOt-Bu	BINAP (0.35)	85	5.0	36
5	$Pd_2(dba)_3$ (0.06)	NaOt-Bu	BINAP (0.17)	85	5.0	12
6	$Pd_2(dba)_3$ (0.25)	NaOt-Bu	BINAP (0.7)	60	5.0	56
7	$Pd_2(dba)_3$ (0.25)	TEA	BINAP (0.7)	85	1.0	No Rxn
8	$Pd_2(dba)_3$ (0.25)	lutidine	BINAP (0.7)	85	1.0	No Rxn
9	$Pd_2(dba)_3$ (0.25)	NaOt-Bu	DPPF (0.7)	85	3	No Rxn
10	$(DPPF)PdCl_2.CH_2Cl_2$(5.0)	NaOt-Bu	DPPF (15)	100	33	66
11	$Pd_2(dba)_3$ (0.25)	NaOt-Bu	PPFA (0.7)	85	1.0	No Rxn
11	$Pd(OAc)_2$ (0.25)	NaOt-Bu	BINAP (0.7)	85	5.0	48

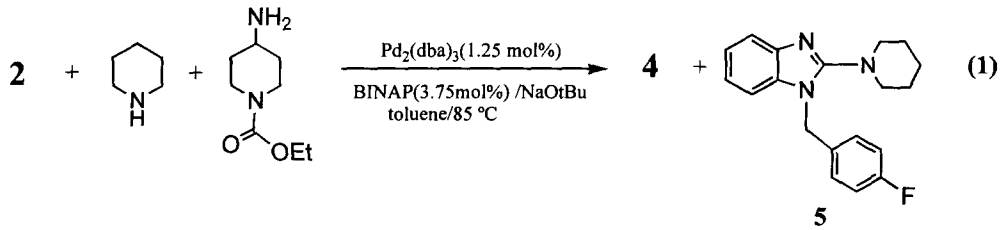
Due to the unique reactivity of the C-Cl bond of **2** under the reaction conditions, we undertook a study on the scope and limitations of the amination process. Surprisingly, secondary cyclic amines displayed an extremely lower reactivity than primary amines. When compound **2** was exposed to piperidine in the presence of 0.25 mol% of $Pd_2(dba)_3$ and 0.75 mol % of BINAP in toluene at 85 °C for 4h, <3% of the desired product **5** was observed (Table 2, entry 1). However, when the reaction is conducted with higher catalytic loading (1.25 mol% of $Pd_2(dba)_3$, 3.75 mol% BINAP), 92% conversion was observed after 20h at 85 °C. The coupling can also be affected with $Pd(OAc)_2$ (4 mol%) and BINAP (6 mol%) at 85 °C to give **5** in 71% yield (>98 % conversion) in 1h (Table 2, entry 5).

Table 2



5

Entry	Pd-catalyst (mol %)	BINAP mol %	Reaction Time h	Conversion %, Yield %
1	$Pd_2(dba)_3$ (0.25)	0.75	4	5, <3
2	$Pd_2(dba)_3$(0.75)	2.25	4	85, 47
3	$Pd_2(dba)_3$(1.25)	3.75	20	94, 70
4	$Pd(OAc)_2$ (2)	3.0	4.5	93, -
5	$Pd(OAc)_2$ (4)	6.0	1	>98, 71



Since the primary amine **3** displays greater reactivity than piperidine at lower catalyst loading, we envisaged selectively coupling **2** with primary amines in the presence of secondary amines. To test this hypothesis, competing experiment shown in Equation 1 was conducted. As expected, upon treatment of a 1:1 molar ratio of **3**:piperidine and **2** under the standard catalytic conditions ($Pd_2(dba)_3$ (0.25 mol%), BINAP (0.75%)) after 2h, 98% conversion with a ratio of 7.7:1 of **4**:**5** was observed. When the reaction was conducted with 1.25 mol% $Pd_2(dba)_3$, 3.75 mol% BINAP, the reaction was complete within 30 min with a ratio of 7.1:1of **4**:**5**.

Scheme 1

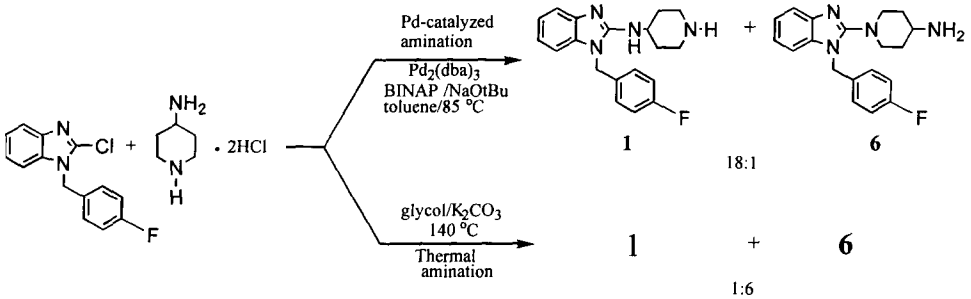
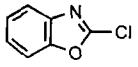
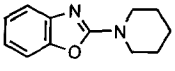
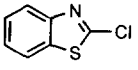
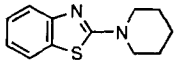
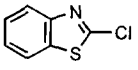
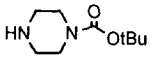
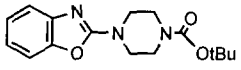
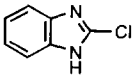
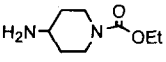
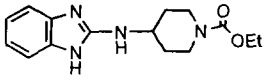
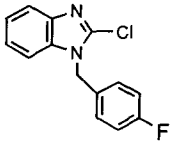
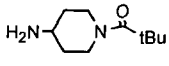
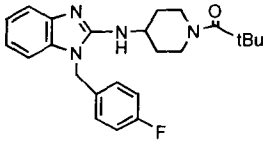


Table 3

entry,	Cl-azole	amines	product	reaction time h	yield %[1] (HPLC conversion
1				1	66(>99)
2				6	78(>99)
3				16	72(>99)
4				10	no Rxn
5				1	68(>95)

1) chromatography yield 2) all reactions were conducted under N_2 atmosphere see reference 11 for procedure

The amine selectivity was extremely valuable for the norastemizole synthesis. When 4-aminopiperidine dihydrochloride was reacted with 4-fluorobenzyl-2-chlorobenzimidazole in the presence of $Pd_2(dba)_3$ (1.25 mol%), BINAP(3.75 mol%)

and 4.2 equivalent of NaOtBu in toluene at 85 °C, a >18:1 ratio of norastemizole (**1**):**6** was obtained.[9] The assay yield for the reaction was 85 wt% for **1**. To the best of our knowledge, this is the first example of a palladium-catalyzed selective coupling of a primary amine in the presence of a secondary amine. It is important to note that the Pd-catalyzed amine coupling selectivity is in contrast to the thermal coupling reaction.[10] When 4-fluorobenzyl-2-chlorobenzimidazole and 4-aminopiperidine are heated in glycol in the presence of K_2CO_3, a 6:1 ratio of **6**:**1** is observed (Scheme 1).

The viability of the amination process was extended to other 1,3-azoles and amines. The preliminary results are shown in Table 3. In most cases, the conversion of the 2-chloro-1,3-azoles to the corresponding 2-amino adducts was >95% with isolated yields varying somewhat.[11] Unprotected chlorobenzimidazole does not couple with the amine even with excess sodium t-butoxide (2.5 equivalents). The protected aminate analog, however, couples with primary or secondary amines without difficulty (entries 4 and 5).[10]

A highly efficient and new palladium-catalyzed amination process for the preparation of the antihistaminic norastemizole was developed. The use of palladium-catalyzed aminations of 2-chloro 1,3-azoles offers a practical method for the preparation of 2-amino-1,3-azoles. Furthermore, palladium-catalyzed chemoselective amination of primary amines in the presence of secondary provides a simple solution to the preparation of synthetically complex and pharmacologically useful aminoazoles. The scope of the palladium-catalyzed selective amination of haloazoles and its mechanism are being explored.

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(8) Beller, M.; Riermeier, T. H.; Reisinger, C.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, 2073.

(9) Surprisingly, upon treatment with 4-aminopiperidine dihydrochloride and **2** under the standard catalytic conditions ($Pd_2(dba)_3$ (0.25 mol%), BINAP (0.75%)) in the presence of 4.2 equivalence of NaOtBu very low reactivity of both amines was observed (17:1 ratio of **1**:**6** with a 85% conversion after 20h).

(10) Unprotected piperazine mono aminations: Zhao, S. H.; Miller, A, K.; Berger, J.; Flippin, L. A. *Tetrahedron Lett.* **1996**, 4463

(11) **A general procedure is as follows:** To a 1L, 3-neck flask equipped with a thermometer, a reflux condenser, an overhead stirrer, an addition funnel under a N_2 atmosphere, 1-(4-fluorobenzyl)-2-chlorobenzimidazole (**2**) (26.1 g, 100 mmol, 1.0 eq.), $Pd_2(dba)_3$ (230 mg, 0.5 mol% Pd), BINAP (470 mg, 0.75 mol%) and tBuONa (13.4 g, 140 mmol) were charged. The resulting mixture is degassed three times followed by addition of toluene (100 mL, anhydrous) and ethyl 4-aminopiperidine carbamate (**3**) (20.5 g, 120 mmol). The mixture bubbled through with N_2 for 2-3 min, heated to 85 °C and stirred at that temperature for 1 h (typically the conversion is >98% monitored by HPLC). The mixture is cooled to 50-60 °C and diluted with 150 mL of heptane. Water (200 mL) was added and stirred at 22 °C for 2 h. After cooling to 0-5 °C, the mixture was stirred at 0-5 °C for 2-3 h. The solid product was collected by vacuum filtration, washed with water (2 x 30 mL) and heptane (2 x 30 mL) and air-dried for 30 min. The wet cake is dried for 6 h at 60 °C/28 inHg to afford 33.4g in 84.3 % yield of norastemizole carbamate (**4**) (chemical purity is 99.7 %). ^{1}H-NMR (300 MHz, $CDCl_3$), d(ppm): 7.53 (1H, d, J=7.8 Hz), 7.22-6.92 (7H, m, two groups), 5.12 (2H, s), 4.37 (1H, NH br. d), 4.12 (2H+1H, m overlapped), 4.07 (2H, q, J=7.0 Hz), 2.98 (2H, t), 2.09 (2H, d), 1.30 (2H, m overlapped), 1.24 (3H, t, J=7.0 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$), d(ppm): 164.2, 161.0 (^{13}C-^{19}F coupling), 155.6, 153.3, 142.2, 134.5, 131.4, 128.3, 121.8, 120.0, 116.6, 116.3, 116.1, 107.5, 61.5, 50.1, 45.0, 42.8, 32.6, 14.8.

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