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Palladium mediated cross-coupling reaction of an heteroaryl-imidoyl chloride and primary amines — preparation of a new ligand of serotoninergic receptors

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Abstract

A new ligand of serotoninergic receptors was synthesized by cross coupling between a triamine and an arylimidoyl chloride. A comparison of the different methods used to make a 'pseudo-amidinic' bond from primary amines and an imidoyl chloride is presented. The best results were obtained using Pd_2dba_3:BINAP catalysis (0.25:0.75%, respectively). © 1999 Elsevier Science Ltd. All rights reserved.

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Serotonin (5-hydroxytryptamine or 5-HT) is involved in a number of physiological and pathological processes in the central and peripheral nervous system.[1] It is also an important target in the development of antidepressant drugs,[2] and of radiotracers to study serotoninergic neurotransmission in vivo using positron emission tomography (PET) or single photon emission tomography.[3] For these reasons, there is still a search for new potent and selective ligands and radioligands of the different 5-HT receptors. Recently, it was shown that the heterocycles **1** and **2** are agonists with a picomolar range of affinity for 5-HT_3 receptors (Scheme 1).[4,5] In our continuing interest for studying serotoninergic neurotransmission[6] and to compare the affinity of both enantiomers of a ligand towards the 5-HT receptors, we chose to synthesize the potential 5-HT ligand **3a** from the heteroaryl chloride **4a** and the amine **5a** which are easily available.[7]

Compounds **1–3** are characterized by a 'pseudo-amidine' function. This group is generally introduced by reaction of an imidoyl chloride with an excess of amine, at high temperatures and for extended periods of time.[6] High-pressures have also been used.[8] These conditions severely limit the scope of the reaction, particularly when the amines are of high cost and when the substrate or the reaction product are sensitive to racemization. Iminotriflates[9] and iminoethers[10] were shown to react cleanly, under mild conditions with primary, secondary amines and aniline to afford the corresponding amino derivatives.

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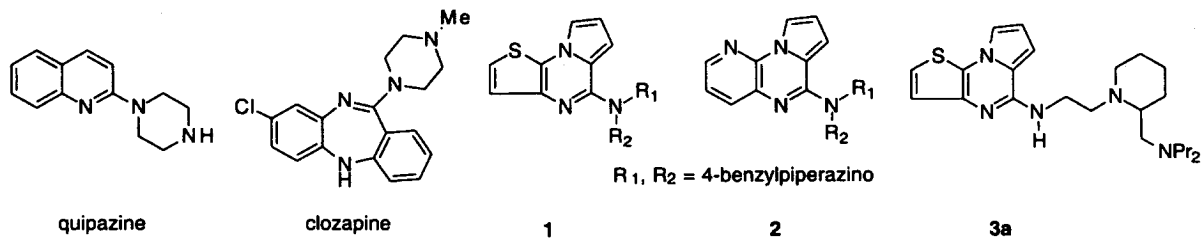
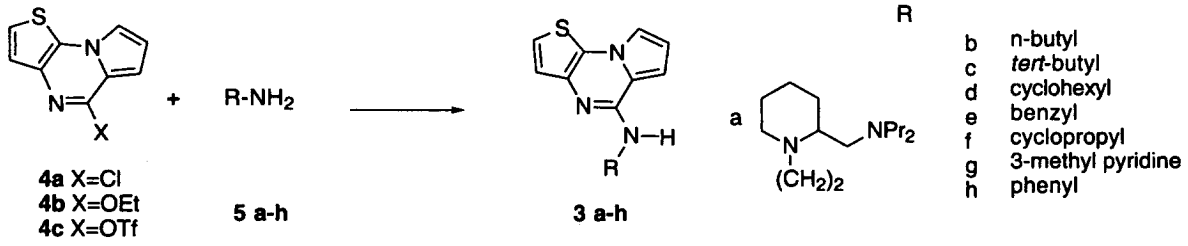


Scheme 1.

In the case of 'pseudo-amidines', being of significant medicinal interest owing to their wide ranging biological activity, there is a need for the development of a general methodology which would allow the synthesis of these compounds under mild conditions. Over the last few years Buchwald[11] and Hartwig[12] have, independently, developed a palladium based methodology to couple amines and halogeno or aryl triflates.

We report here the synthesis of new 'pseudo-amidines', especially the coupling of the heteroaryl-imidoyl chloride **4a** with the triamine **5a** to prepare the target compound **3a** (Scheme 2).



Scheme 2.

Previously, the imidoyl chloride **4a** reacted successfully with secondary amines (piperidine, piperazines and morpholine) under thermal conditions.[5] In our first attempts, we chose a primary amine, *n*-butylamine **5b**, as a cheap substitute of triamine **5a**, to study its coupling with the chloride **4a**,[5] the iminoether **4b**[13] or the triflate **4c**[14] under selected conditions. Table 1 summarizes the most representative results.

Under classical thermal conditions, **3b** was formed in yields lower than 46% (entries 1–3). Moreover, the reaction required 5 equivalents of butylamine. This excess can be a major drawback if expensive amines have to be coupled. Similar yields were obtained starting from the heteroaryl triflate **4c** (entries 6 and 7). All attempts for coupling the triamine **5a** with the imidoyl chloride **4a** or the triflate **4c**, under the conditions described for *n*-butylamine (Table 1, entries 3 and 6, respectively) failed to yield the pseudo-amidine **3a**.

The palladium catalyzed amination of imidoyl halides has been successful with 2-bromopyridine,[15] 2-chlorobenzimidazole[16] and 6-chloropurine[17] derivatives, these substrates also being known to react with primary amines under non-catalyzed conditions. To study the cross-coupling of chloride **4a** with *n*-butylamine, we initially employed Pd_2dba_3:BINAP (0.5:1.5%, respectively) as the catalyst with *t*BuONa as the base in toluene at 80°C. After 14 h, **3b** was isolated within a 90% yield. Based on the same protocol, several primary amines were appended on imidoyl chloride **4a** under various conditions of time and temperature. Results are presented in Table 2.

All reactions afforded coupling products in good to excellent yield. High temperatures showed a small influence on the yield (entries 3 and 4) but significantly reduced the reaction time (Table 2, entries 3 and 4). *tert*-Butylamine, a highly branched primary amine (entry 2) still gave the coupling product in

Table 1
Uncatalyzed reactions of heteroaryl **4** with *n*-butylamine **5b** to yield **3b**

entry	compound	n-Bu-NH_2, nb eq.	solvent	T (° C)	time	Conditions	Yield (%)[a]
1	**4a**	10	THF	65	7 d	-	17
2	**4a**	5	toluene	110	24 h	BuLi (5 eq)[b]	20
3	**4a**	5	«	110	5 d	Sealed tube	46
4	**4a**	1	THF	TA	48 h	NEt_3 (2 eq)/10 kbars	7
5	**4b**	2	EtOH	90	2 d	pTsOH cat.	traces
6	**4c**	2.2	DMSO	40	14 h	-	40
7	**4c**	1.2	«	40	14 h	Et_3N (2 eq)	30

[a] isolated yield.
[b] n-butylamine and n-butyllithium in hexane were mixed at 0°C.

Table 2
Palladium catalyzed reaction of chloride **4a** and primary amines **5** to yield 'pseudo-amidines' **3**

entry	amine		solvent	temp. (°C)	time (h)	product	Yield[a]
1[b]	n-butyl-NH_2	**5b**	toluene	110	15	**3b**	94
2[b]	tert-butyl-NH_2[c]	**5c**	xylenes	130	24	**3c**	65
3	cyclohexyl-NH_2	**5d**	toluene	110	18	**3d**	90
4	cyclohexyl-NH_2	**5d**	xylenes	130	1	**3d**	83
5	benzyl-NH_2	**5e**	«	«	1	**3e**	93
6	cyclopropyl-NH_2	**5f**	toluene	110	15	**3f**	87[d]
7	3-aminomethyl pyridine	**5g**	xylenes	130	1	**3g**	72
8	aniline	**5h**	«	«	15	**3h**	83
9	triamine	**5a**	«	«	1	**3a**	85[e]

[a] General experimental conditions : to a mixture of chloroimine (1 mmol), Pd_2dba_3 (2.5 µmol), BINAP (7.5 µmol) and primary amine (1.2 mmol) in 5 ml of a degassed solvent was added tBuONa (1.4 mmol) under nitrogen. The time and reaction temperature are listed in the table. The products are purified by flash chromatography on silica gel .
[b] reaction carried out in a sealed tube.
[c] 4 mmol of amine was used .
[d] unstable product .
[e] 5 µmol of Pd_2dba_3 and 15 µmol of BINAP were used.

reasonable yield. Finally, the target compound **3a** (entry 9) was isolated within an 85% yield. Pd_2dba_3 consistently gave better results than $Pd(OAc)_2$. Using $P(oTol)_3$ instead of BINAP as the phosphine ligand did not lead to any coupling product of **4a** with the aliphatic primary amines **5**.

This work provides a useful comparison of different methods used to make a 'pseudo-amidinic' bond from primary amines and an heteroaryl chloride. We have demonstrated the superior synthetic utility of the palladium based cross coupling methodology. This should find wide application in medicinal chemistry where these bonds are frequently encountered.[18] The conditions described are particularly

attractive for unreactive arylimidoylchloride, expensive amines and because a small amount of palladium catalyst is used.

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