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A two-step synthesis of aminopropylpiperidines via aminopropargylpyridines, suitable for the synthesis of a new class of 5-HT$_4$ ligands

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Abstract—A rapid and flexible synthetic approach to {[bis(*tert*-butoxycarbonyl)amino]propyl}piperidines **5** and related compounds is described. The key step is a three-component coupling process of 2-, 3- or 4-bromopyridine, propargyl bromide and potassium di-*tert*-butyliminodicarbonate under palladium–copper catalysis leading to 2-, 3- or 4-{[bis(*tert*-butoxycarbonyl)amino]-propargyl}pyridines **4** followed by a catalytic reduction step.
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The 5-HT$_4$ receptor, which belongs to the superfamily of G protein-coupled receptor (GPCR) is implicated in a wide variety of pathological disorders. A body of evidences suggests that this receptor represents a valuable therapeutic target for the cure of diseases of importance stimulating the active research of new drugs.[1] Current targets concern atryal arrhythmia, irritable bowel syndrome, dysfunction of the urinary tract, memory troubles and the role of 5-HT$_4$ receptors in Alzheimer disease seems now well established.[2] Besides the 5-HT$_4$ ligands available to date,[1] our aim was to rationalize the synthesis of a new class of 5-HT$_4$ ligands in favouring interactions with targeted amino acids of the receptor. The design is based on directed mutagenesis and molecular modelling studies, identifying amino acids of the binding site and interactions involved in the ligand–receptor recognition.[3] Particularly, a thorough delineation of the binding crevice has localized a large hydrophobic pocket[4] containing two polar amino acids able to interact with bulky ligands. Consequently, on the pharmacophore of 5-HT$_4$ ligands, featured by an aromatic moiety, a carbonyl function and a basic nitrogen atom generally included in a piperidine ring, the substitution of this ring by functionalized chains could enhance the possible anchor points of the ligand in the binding site and more particularly in the large hydrophobic pocket. We then decided to synthesize new 5-HT$_4$ ligands containing aminoalkylpiperidine groups and in particular primary, secondary or tertiary functionalized aminopropylpiperidine.

For this purpose, aiming at developing combinatorial strategies to quickly access to a library of 5-HT$_4$ ligand compounds, we required a rapid route to a variety of protected aminopropylpiperidines **5** (Scheme 1). In order to differentiate the two amino groups of these scaffolds, the amino function of the alkyl chain should be protected. In this context, *tert*-butoxycarbonyl (Boc) appears a protecting group of choice because of the easiness of its removal under mild conditions.

A survey of the literature revealed that only two reports on the preparation of aminopropylpiperidines have been described. The first one involves reduction of aminal compounds[5] and the second one is based on the reaction

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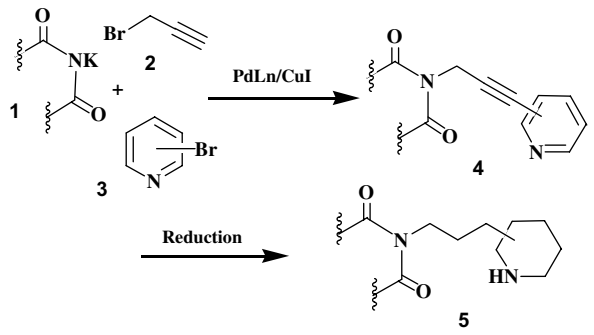


Scheme 1.

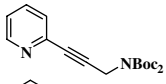
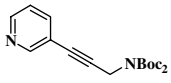
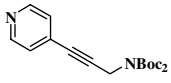
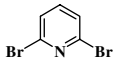
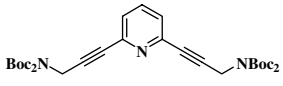
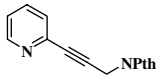
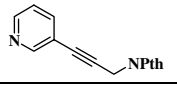
of (dialkylamino)ethyl chloride with picolyllithiums followed by a catalytic hydrogenation.[6] Both approaches however, required the preparation of starting materials and are not suitable for the synthesis of protected aminopropylpiperidines **5**. This background prompted us to concentrate on the development of a simple method for their preparation. Herein we wish to report our preliminary results towards a rapid and highly flexible synthesis of 2-, 3- and 4-{[bis(*tert*-butoxycarbonyl)-amino]propyl}piperidine compounds **5**. The strategy depicted in Scheme 1 involves a two-step sequence based on a three-component Sonogashira–Linstrumelle[7] type coupling process from commercially available substrates **1**–**3** leading to protected aminopropargylpyridines **4** followed by a catalytic reduction step.

Very recently, we reported a three-component coupling of propargyl halides, aryl halides and a secondary amine used as solvent for the direct access to a variety of substituted propargylic amines.[8] It was interesting to examine if this coupling procedure could be extended to the synthesis of protected aminopropargylpyridines **4** from readily available potassium phthalimide or potassium di-*tert*-butyliminodicarbonate. These later represent useful reagents for the introduction of protected amino function into organic compounds, easily and selectively removed for obtaining secondary and primary amines. Subsequent reduction of both the pyridyl ring and the triple bond of **4** would provide the target structure **5**.

According to Scheme 1, potassium di-*tert*-butyliminodicarbonate was reacted with propargyl bromide in DMF at room temperature for 2 h. Then, 2-bromopyridine, triethylamine, bis(triphenylphosphine)palladium chloride and copper iodide were added into the reaction mixture and the temperature was raised to 80 °C for 24 h. Under these conditions, the three-component coupling product **4a** was obtained in almost quantitative yield[10] (Table 1, 93%, entry 1). Similarly, the coupling reaction with 3- or 4-bromopyridine as well as with 2,6-dibromopyridine afforded the coupling products **4b–d** in good yields (entries 2–4). This three-component coupling process was also effective when using potassium phthalimide instead of potassium di-*tert*-butyl imino-dicarbonate (entries 5 and 6).

In order to obtain primary and secondary propargylamine compounds **6** and **7** for further selective modifications, we have also studied the deprotection of the amino function of compounds **4** (Table 2). To our knowledge, such building blocks having a primary or a secondary amine function are unknown in the literature. Thus, hydrolysis of phthalylpropargylamine **4e** with hydrazine hydrate[11] in EtOH gave the primary propargylamine **6a** in 63% yields[12] (Table 2, entry 1). The cor-

Table 1. Synthesis of protected aminopropargylpyridines **4** via a three-component coupling procedure[a]

Entry	RBr	Amine salts	Coupling product **4**[b]		Yield (%)[c]
1		$KN(Boc)_2$		**4a**	93
2		$KN(Boc)_2$		**4b**	74
3		$KN(Boc)_2$		**4c**	82
4		$KN(Boc)_2$		**4d**	53[d]
5		KNPth		**4e**	82
6		KNPth		**4f**	50

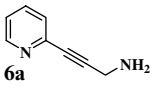
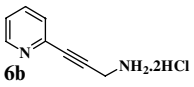
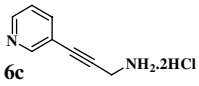
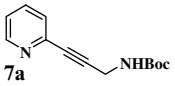
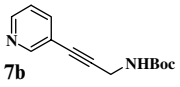
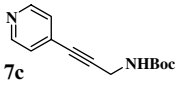
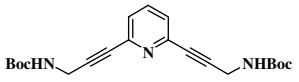
[a] All reaction were carried out with RBr (1 equiv), amine salts (2 equiv), propargyl bromide (2 equiv), Et_3N (10 equiv), CuI (10 mol%), $PdCl_2(PPh_3)_2$ (5 mol%) in DMF at 80 °C. For a general procedure see Ref. 9.

[b] All protected aminopropargyl pyridine derivatives synthesized **4** are new compounds and exhibited satisfactory spectral properties.

[c] Isolated yield based on bromopyridine.

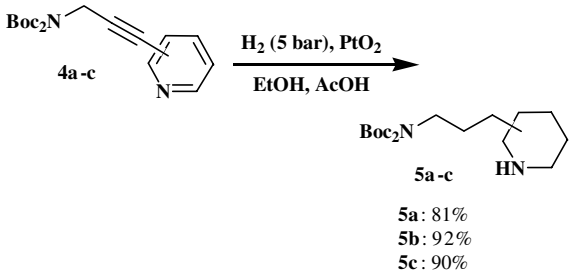
[d] Amine salts (4 equiv) and propargyl bromide (4 equiv) were used.

Table 2. Synthesis of primary and secondary aminopropargyl pyridine derivatives **6** and **7**

Entry	Reactant/ conditions[a]	Deprotected product[b]	Yield (%)[c]
1	**4e**/A	 **6a**	63
2	**4a**/B	 **6b**	94
3	**4b**/B	 **6c**	95
4	**4a**/C	 **7a**	73
5	**4b**/C	 **7b**	75
6	**4c**/C	 **7c**	71
7	**4d**/C	 **7d**	65

[a] Conditions A: hydrazine hydrate (4 equiv), EtOH, 70 °C, 30 min; B: HCl/MeOH 4 N, 20 °C, 1.5 h, C: LiBr (3 equiv), MeCN, 65 °C, 14 h.
[b] Compounds **6** and **7** are new derivatives and exhibited satisfactory spectral properties.[16]
[c] Isolated yield based on starting materials **4**.

responding hydrochloride derivative **6b** as well as compound **6c** were obtained in almost quantitative yield (94–95%, entries 2 and 3) when performing the deprotection step under acidic conditions in the presence of HCl/MeOH.[13] It should be noted, that this two step strategy for the synthesis of **6a** and **6b** based on the above three-component coupling process followed by a deprotection step provides a much more powerful and efficient alternative than the direct Sonogashira–Linstrumelle coupling reaction. Indeed, attempts coupling of 2-bromopyridine with commercially available propargylamine at room temperature using various combinations of palladium catalyst and amines (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2Et_2NH$, Et_3N, piperidine with or without CuI)[14] resulted in unsatisfactory yields certainly due to the instability of the resulting compound **6a** under the conditions used. On the other hand, selective monodeprotection of compounds **4a**–**d** was also examined under the recent report of Hernandez et al.[15] Thus, when using LiBr in MeCN secondary aminopropargylpyridines **7a**–**d** were obtained in good yields (65–73%, entries 4–7). It is important to note that functionalization of the nitrogen atom of compounds **6** and **7** by one or two different critical functionalized chains could be of considerable interest to interact specifically with targeted identified amino acid residues.[4]



Scheme 2.

Finally, according to our strategy, the catalytic hydrogenation of 2-, 3- or 4-{[bis(*tert*-butoxycarbonyl)-amino]propargyl}pyridines **4a**–**c** was performed in the presence of platinum oxide[6] and afforded in excellent yields (81–92%, Scheme 2) the reduced products **5a**–**c** making our two-step approach very efficient for the synthesis of protected aminopropylpiperidine derivatives.[17]

In conclusion, we have demonstrated that this two-step sequence based on a three-component Sonogashira–Linstrumelle type coupling reaction leading to protected aminopropargylpyridines **4** followed by a catalytic hydrogenation represents an efficient and rapid route to protected aminopropylpiperidines **5**. These later would be key intermediates for the solid support synthesis of a new family of 5-HT_4 ligands. Moreover, the high flexibility of this strategy allows the substitution of the aminopropyl group as well as the functionalization of the carbon–carbon triple bond of the propargyl function by pertinent chains able to interact with targeted amino acid residues of the hydrophobic pocket of the binding site. The synthesis of libraries is now in progress and will further be pharmacologically evaluated.

Acknowledgements

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9. General procedure for the three-component coupling reaction: To a suspension of $KNBoc_2$ (1.59 g, 6.24 mmol) in freshly distilled DMF (15 mL) was added at 0 °C propargyl bromide (695 μL of a 80% wt solution in toluene purchased from Aldrich, 6.24 mmol). After stirring at room temperature for 2 h, the mixture was added to a solution of $PdCl_2(PPh_3)_2$ (109 mg, 5 mol%), CuI (59 mg, 10 mol%), 2-bromopyridine (301 μL, 3.12 mmol) and Et_3N (4.3 mL, 24.94 mmol) via a cannula and heated at 80 °C for 24 h. The solvents were removed under vacuum, and the residue was dissolved in CH_2Cl_2, filtered through a pad of celite and concentrated. Purification by silica gel chromatography gave 970 mg (93%) of pure **4a**.
N,N-Di-tert-butoxycarbonyl-3-pyridin-2-ylprop-2-ynyl amine (**4a**) $R_f = 0.30$ (cyclohexane/AcOEt 7/3); mp (white solid) 71–73 °C (*i*Pr_2O/pentane); ^1H NMR (200 MHz, $CDCl_3$): δ 8.53 (d, $J = 4.9$ Hz, 1H), 7.60 (td, $J = 7.7$ and 1.8 Hz, 1H), 7.35 (d, $J = 7.7$ Hz, 1H), 7.19 (td, $J = 4.9$ and 1.8 Hz, 1H), 4.60 (s, 2H), 1.52 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.6, 150.0, 143.2, 136.1, 127.2, 122.8, 85.6, 83.1, 81.9, 36.5, 28.2.
The same procedure using potassium phthalimide (1.16 g, 6.24 mmol) gave 670 mg (82%) of pure **4b**. *N-Phthalyl-3-pyridin-2-ylprop-2-ynylamine* (**4b**): $R_f = 0.12$ (cyclohexane/AcOEt 7/3); mp 127–129 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 8.50 (d, $J = 4.9$ Hz, 1H), 7.87–7.69 (m, 4H), 7.59 (td, $J = 7.7$ and 1.8 Hz, 1H), 7.37 (d, $J = 7.7$ Hz, 1H), 7.18 (td, $J = 4.9$ and 1.8 Hz, 1H), 4.68 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.0, 150.0, 142.7, 136.2, 134.3, 132.0, 127.3, 123.6, 123.2, 85.2, 82.9, 26.9.
10. Attempts obtention of **4a** by coupling of 3-pyridin-2-ylprop-2-yn-1-ol with $HNBoc_2$ under Mitsunobu conditions (DEAD or DIAD, PPh_3 in THF) resulted however in unsuccessfull results.
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16. *3-Pyridin-2-yl-prop-2-ynylamine* (**6b**) $R_f = 0.19$ (AcOEt/$MeOH/NH_4OH_{aq}$, 20% 87/10/3); ^1H NMR (CD_3OD, 200 MHz): δ 8.62 (b s, 1H), 7.92 (t, $J = 7.7$ Hz, 1H), 7.64 (m, 1H), 7.51 (m, 1H), 4.09 (s, 2H). ^{13}C NMR (CD_3OD, 50 MHz): δ 149.0, 141.3, 140.4, 130.2, 126.5, 85.6, 84.0, 30.5.
17. *N,N-Di-tert-butyloxycarbonyl-3-piperidin-3-yl-propyl-amine* (**5b**) $R_f = 0.21$ (AcOEt/$MeOH/NH_4OH_{aq}$ 20% 87/10/3); ^1H NMR ($CDCl_3$, 200 MHz): δ 3.51 (t, $J = 7.5$ Hz, 2H), 3.00 (m, 2H), 2.50 (td, $J = 11.8$ and 2.8 Hz, 1H), 2.21 (b t, $J = 11.8$ Hz, 1H), 2.03 (b s, 1H), 1.81 (m, 1H), 1.70–1.33 (m, 22H), 1.30–0.78 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.9, 82.2, 53.1, 47.1, 46.8, 37.0, 31.7, 28.2, 26.7, 26.3, 17.8.