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A versatile protocol for the preparation of substituted 1- and 2-naphthyl piperazines from aminonaphthols

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Abstract—Aminonaphthols are easily transformed into a variety of 1- and 2-naphthyl piperazines using a sequence of diazotization, iodide substitution and Pd(0) catalyzed coupling reactions.
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1. Introduction

Naphthyl piperazines are known ligands for several CNS targets, including serotonin (5-HT)[1] and dopamine receptors.[2] During the course of our studies of naphthyl piperazines as inhibitors of the 5-HT transporter,[3] we became interested in the evaluation of 5-, 6-, 7- and 8-substituted 1- and 2-naphthyl piperazines of general formula I and II (Fig. 1).

A general method to obtain these systems is not available. The most widely used approach is the Semmel–Wolff reaction[4] that relies on the formation of an oxime from a tetralone, oxidation to the aminonaphthalene and subsequent conversion of the amine to a piperazine.[5] Alternative approaches from tetralones have also been reported (Scheme 1).[6,7]

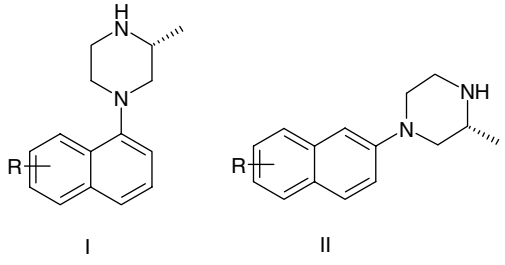

Figure 1.

Despite the low yields reported, this is a valuable method; but it is restricted by the limited number of commercially available tetralones. However we recognized that many regioisomeric aminonaphthols could be purchased, or could be accessed in a single step from commercially available naphthalenes,[8] though to date they had not been used as starting materials for the synthesis of substituted naphthyl piperazines. We reasoned that the use of two powerful reactions, the diazotization of amines[9] and the transition metal catalyzed coupling of halogens/triflates with piperazines,[10] could give us the versatility needed for the incorporation of a variety of substituents on the naphthalene moiety.

In this paper we disclose the results obtained with this versatile synthetic route to 5- and 6-substituted 1-naphthyl piperazines, and 5- and 8-substituted 2-naphthyl piperazines, using aminonaphthols as starting materials.

2. Results and discussion

The generation of diazonium salts from aromatic amines and their subsequent decomposition to aromatic iodides, chlorides, fluorides, alcohols, sulfonyl chlorides, nitriles, azides and aldehydes is well documented in the

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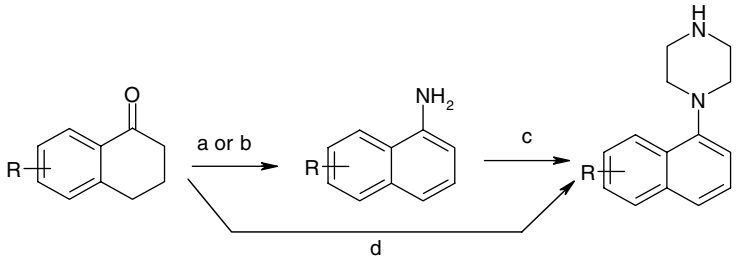


Scheme 1. Reagents and conditions: (a) i. NH_2OH, ii. HCl, AcOH, Ac_2O, 100 °C, 26–68% overall yield (Ref. 4); (b) i. $BnNH_2$, ii. Pd–C 31–42% overall yield (Ref. 6); (c) $(ClCH_2CH_2)_2NH$, base; (d) i. piperazine, *p*-TsOH, ii. Pd–C. Overall yield not reported (Ref. 7).

literature.[9] For the synthesis of I and II, we envisioned a retrosynthetic scheme based on the diazotization of an amine for the installation of the substituent R in replacement of the nitrogen, and a Pd(0) catalyzed coupling for the installation of the piperazine in replacement of the alcohol (Scheme 2).

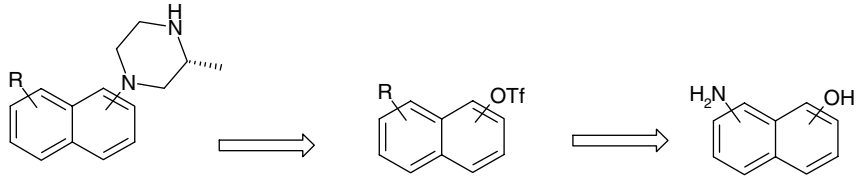
The reaction of 6-amino-1-naphthol with $NaNO_2/H^+$, followed by controlled decomposition of the diazonium salt with CuCl under standard conditions[11] provided the chloro derivative in only 21% yield, with dimers being obtained as side products. Although such diazotization reactions have been described for phenols,[12] we decided to protect the alcohol. Thus the reaction of 6-amino-1-naphthol with *N*-phenyl trifluoromethanesulfonimide provided the corresponding triflate **2a** in good yield. Subsequent reaction with $NaNO_2/H^+$, followed by treatment with CuCl or KI, provided the corresponding 6-chloro and 6-iodo naphthyl triflates **3a** and **3b**, respectively (Scheme 3).

Compound **3b** could then be further elaborated to other functional groups. Thus lithium–halogen exchange of the iodide, followed by treatment with $FN(SO_2Ph)_2$ or with $MeSSO_2Me$, provided compounds **3c** and **3f** in 40% and 65% yield, respectively. Cyanation of **3b** with NaCN catalyzed by palladium (0) provided the nitrile derivative **3d** in 45% yield. Copper catalyzed reaction of **3b** with $FSO_2CF_2CO_2Me$ provided compound **3e** in 52% yield. Although the direct decomposition of the diazonium salt with suitable reagents could give rise to compounds **3c–f** from **2a** in a single step, the two-step procedure via the halide proved more suitable for our needs (Scheme 3).

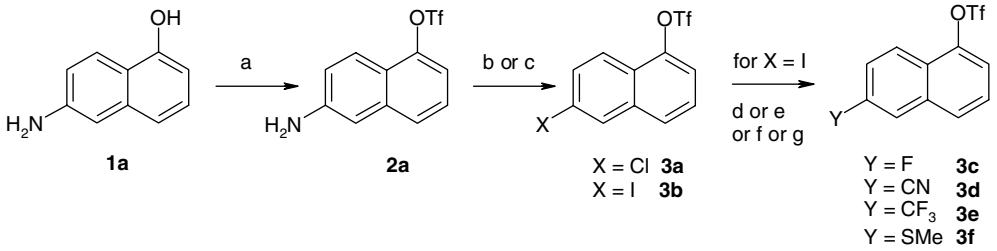
It is worth noting how the triflate can act as a protecting group in a variety of reactions (diazotization, metal–halogen exchange, palladium catalyzed cyanation) without decomposition or side reactions.

The results obtained for the synthesis of other naphthyl triflates are collected in Table 1.

The naphthyl triflates were subsequently coupled with (*R*)-2-methylpiperazine under standard palladium-catalyzed conditions,[13] providing the naphthyl piperazines in variable yields, depending on the reaction conditions and the nature of the starting material.[14] When a monoprotected piperazine was used instead in the coupling step, yields were moderate but more reliable,

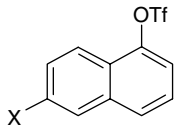
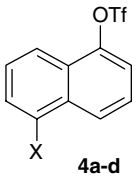
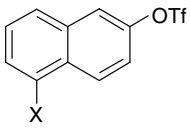
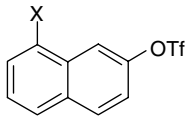


Scheme 2.

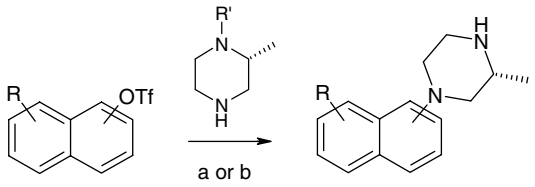


Scheme 3. Reagents and conditions: (a) $PhN(SO_2CF_3)_2$, NaO*t*-Bu, THF, 0 °C (94%); (b) i. HCl, H_2O, $NaNO_2$, ii. CuCl, H_2O (52%); (c) i. HCl, H_2O, $NaNO_2$, ii. KI, H_2O (74%); (d) *t*-BuLi (2×), $FN(SO_2Ph)_2$, THF, −78 °C to rt (40%); (e) CuI, $Pd(PPh_3)_4$, NaCN, THF, reflux (41%); (f) $FSO_2CF_2CO_2Me$, CuI, DMF (52%); (g) *t*-BuLi (2×), $MeSSO_2Me$, THF, −78 °C to rt (65%).

Table 1. Synthesis of substituted naphthyl triflates from aminonaphthols[a]

	 3a-e	 4a-d	 5a-d	 6a-e
I	70%	70%	77%	77%
Cl	49%	70%	65%	55%
F	28%	28%	30%	63%
CN	31%	28%	56%	72%
CF_3	36%	—[b]	—[b]	45%

[a] Overall yield from the aminonaphthol.
[b] Not synthesized.



Scheme 4. Reagents and conditions: (a) for $R' = H$: $Pd(OAc)_2$, BINAP, NaO*t*-Bu, toluene, 100 °C (30–95%); (b) for $R' = COCF_3$: i. $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C, ii. $NaBH_4$, EtOH (60–65%).

although an extra deprotection step had to be performed (Scheme 4).

In summary, substituted naphthyl piperazines can be easily accessed by a four step process that relies on the diazotization of aromatic amines; the versatility of aryl iodides for incorporation of varied functionality; and the Pd(0) catalyzed coupling of triflates.

Acknowledgement

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14. Best yields were obtained using the following conditions: 1 M triflate concentration in reaction mixture, 1.2 equiv of 2-methyl piperazine, 1.4 equiv of sodium *tert*-butoxide, 5 mol % palladium catalyst, 1.4 equiv of racemic BINAP relative to palladium, 48 h at 100 °C stirring under N_2 atmosphere, using thoroughly degassed anhydrous toluene as solvent.