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Formation of Phenylpiperazines by a Novel Alumina Supported Bis-Alkylation.

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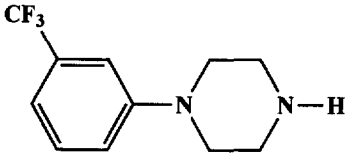
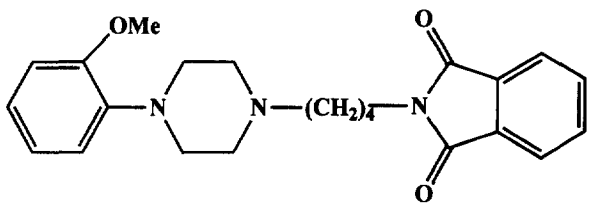
Abstract :The phenylpiperazine ring which could not be obtained by reacting aniline derivatives with bis(2-bromoethyl)-N-(ethoxycarbonyl)amine (**1a**) in a wide spectrum of solvents and temperatures was synthesized rapidly on solid support in high yield. By this approach the potent serotonin agonist TFMPP (**2**) was synthesized in 40 min. in 80% yield. The time scale of this reaction and the simplicity of the work-up match the requirements for short lived neurological radiopharmaceutical production.

An interesting family of compounds in the field of neuropharmaceuticals is arylpiperazines, a common structural feature of many neurological ligands. For example, amongst agents that bind at the various 5-HT_1 (5-hydroxytryptamine) sites, compounds containing arylpiperazines are the most notable.[1] Trifluoromethyl phenylpiperazine[2] (TFMPP, **2**), and NAN-190[3] (**3**) are two examples of the potent serotonin ligands that were built on the arylpiperazine structure (scheme 1).[4] Typically, this class of compounds had been obtained by ring closure of appropriately substituted anilines and bis(2-chloroethyl)amine hydrochloride (**1b**) in the presence of base.[5] Yields of around 40% are obtained after a long reaction time of more than 50 hours.

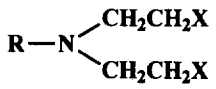
Scheme 1



2 : TFMPP



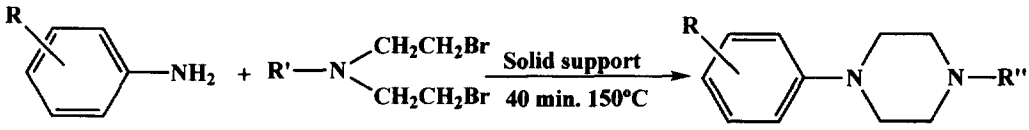
3 : NAN-190



1a : X = Br, R = EtOCO
1b : X = Cl, R = H
1c : X = Br, R = Me
1d : X = OTs, R = Ts

As part of our current research interests, we needed to develop a synthetic route to arylpiperazines that was commensurate with the time limitations imposed by the use of short-lived radioisotopes. Bis(2-bromoethyl)-N-(ethoxycarbonyl)amine (**1a**) is a useful reagent in the synthesis of 4,4-disubstituted piperidines.[6] However, this reagent could not be applied to the synthesis of arylpiperazines in a wide variety of solvents.[7] Therefore, we decided to react the aniline derivatives with **1a** as both the reagent and the solvent on solid surface.[8] The results are summarized in table 1.

Scheme 2



4 : R = H
6 : R = p-F
8 : R = m-CF_3

1a : R' = EtOCO
1c : R' = Me

2 : R = m-CF_3, R'' = H
5 : R = H, R'' = H
7 : R = p-F, R'' = H
9 : R = m-CF_3, R'' = Me

Table 1

Aniline No.	Reagent	Solid S.	Product No. (% yield)
4 (R = H)	1a	—	5 (2-5%)[a]
4	1a	Silica	5 (25%)[a]
4	1a	Alumina	5 (25%)[a]
4	1a	Basic alum.	5 (80%)[a]
6 (R = p-F)	1a	Basic alum.	7 (75%)[a]
8 (R = m-CF_3)	1a	Basic alum.	2 (80%)[a]
8	1c	Basic alum.	9 (70%)[b]

a. Identification of the product and yield determination were done by injection of an authentic standard on HPLC.
b. Yield was calculated after purification on silica column. Identification by ^{1}H NMR (ppm): 7.36(1H, t, J = 7.6Hz), 7.1(3H, m), 3.27(4H, m), 2.6(4H, m), 2.37(3H, s).

The yield after 40 min. reaction of **4** with **1a** as reagent and solvent without any solid support was very low. Increasing the reaction time or the temperature resulted in decomposition of the reactants. Using silica (surface pH=7, high activity grade, particle size 55-105 μm) as solid support to absorb the reactants and to lower the entropy of activation increased the yield. By extracting the mixture with basic methanol the N-substituted intermediate was hydrolyzed to give the phenylpiperazine (**5**) in 25% yield. Increasing either the temperature or the reaction time when using silica as solid support did not improve the yield. Similar results

were obtained on neutral alumina surface having a particle size of 50-300 μm. The best results were obtained with basic alumina (surface pH=9-10, activity grade 1, pore size 120 Å, particle size 50-300 μm) as the solid support. Active alumina is known from spectroscopic studies to cleave the heteroatom-H bonds in primary and secondary amines providing activation of the aniline.[9] Moreover, the HBr liberated after the first bromo replacement is scavenged on the basic alumina freeing the nitrogen to undergo a second intramolecular nucleophilic attack and the yield increased to 70-80%. The presence of an electron withdrawing group on the aromatic ring did not affect the yield. As an example, the potent serotonin agonist TFMPP (**2**) was obtained in 80% yield after 40 minutes. In the same manner N-substituted phenylpiperazines can also be obtained in one step by reacting different N-substituted dibromo derivatives[10] such as **1c**. Reaction of m-trifluoromethyl aniline (**8**) with **1c**, for example, gave the N-substituted phenylpiperazine **9** in 70% yield.

Potent neurological ligands like TFMPP (**2**) can be labeled with positron emitting isotopes providing receptor imaging by the non-invasive Positron Emission Tomography (PET) technique.[11] Moreover, investigation of neurochemical mechanisms of disease in the human living brain and *in vivo* studies of drug pharmacokinetics have been performed by this method.[12] The new synthetic approach to phenylpiperazine described here is applicable for the chemistry of short lived positron emitting isotopes such as ^{11}C, and ^{18}F ($t_{1/2}$ = 20.4, 110 min. respectively) used in PET.

Arylpiperazines have been previously synthesized by reacting aniline derivatives with N,O,O'-tris(toluene-p-sulfonyl)bis(2-hydroxyethyl)amine[7] (**1d**). This reaction gave the product as an N-Tosylated species which requires further synthetic and work-up manipulation to obtain the desired product. The advantage of our procedure is that it directly furnishes the desired N-H, or N-substituted phenylpiperazines with minimal work-up. This is an important consideration for application to PET radiopharmaceutical chemistry where time constraints play an important role in influencing the choice of synthetic route.

The synthesis of product **9** provides an example of the method: 30 mg (0.2 mmol) of m-trifluoromethyl aniline (**8**) and 70 mg (0.4 mmol) of bis(2-bromoethyl)-N-(methyl)amine (**1c**) were added in ether (3 mL) solution to a small flask containing 300 mg of basic alumina (Waters Sep-Pak cartridge 51820, physical and chemical characteristics have been described above). The mixture was vortexed and the ether evaporated with a gentle stream of nitrogen. The flask was capped and heated on a heating block for 40 min. at 150°C. After cooling, the crude product was extracted with 1.5 mL of basic methanol (0.1 mL of NaOH (10N) in 1 mL MeOH) and 1 mL CH_2Cl_2. The solution was filtered through a nylon acrodisc 0.45 micron filter and then purified by silica flash column chromatography (eluent: MeOH:CH_2Cl_2 3:97, containg 0.1% NH_4OH) to give 31 mg (70% yield) of product **9**.

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References

1. Glennon, R. A.; Naiman, N. A.; Pierson, M. E.; Titeler, M.; Lyon, R. A.; Herndon, J. L.; Misenheiner, B. *Drug Dev. Res.* **1989**, *16*, 335. Murasaki, M.; Miura, S. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1992**, *16*, 833
2. Fuller, R. W.; Maso, N. R.; Molloy, B. B. *Biochem. Pharmacol.* **1980**, *29*, 833.
3. Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1.
4. Glennon, R. A.; Naiman, N. A.; Pierson, M. E.; Titeler, M.; Lyon, R. A.; Weisberg, E. *Eur. J. Pharmacol.* **1989**, *154*, 339
5. Kiritsy, J. A.; Yung, D. K.; Mathony, D. E. *J. Med. Chem.* **1978**, *21*, 1301.
6. Huybrechts, S.; Hoornaert, G. J. *Syn. Commun.* **1981**, *11*, 17.
7. Collins, M.; Lasne, M.; Barre, L. *J. Chem. Soc. Perkin Trans 1* **1992**, 1301.
8. Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208, 8214. Posner, G. H. *Angew. Chem. Int. Ed. Eng.* **1978**, *17*, 487.
9. Parera, J. M.; Figoli, J. *Catal.* **1969**, *14*, 303.
10. Pettit, G. R.; Chamberland, M. R.; Blonda, D. S. *Can. J. of Chem.* **1964**, *42*, 1699.
11. Bonab, A. A.; Babich, R. J.; Callahan, N. M. A. *J. Nuc. Med.* **1995**, *36*, 15P.
12. Långström, B.; Hartving, P. In *Radiopharmaceuticals: Chemistry and Pharmacology*; Nunn, A. D., Ed.; Marcel Dekker: New York, 1992; Vol. 55.

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