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Rapid and Efficient Synthesis of 1-Arylpiperazines under Microwave Irradiation

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Abstract : 1-Arylpiperazines, finding wide applicability in pharmaceuticals were synthesized easily under microwave irradiation from bis(2-chloroethyl)amine hydrochloride and substituted anilines without any solvent. The reaction time was just 1-3 mins. 1-Arylpiperazines were synthesized in 53 to 73% yields. Potent serotonin ligands like Trifluoromethylphenylpiperazine (TFMPP) and 3-Chlorophenylpiperazine (mCPP) were also prepared in just 1 min. and 2 mins. respectively.

Phenylpiperazine derivatives possess antihistaminic, antihypertensive, adrenolytic, and antiinflammatory activities.[1] They are also an important class of compounds in the field of neuropharmaceuticals.[2] They bind with high affinity to serotonin sites.[3,4] 1-[3-(trifluoromethyl)phenyl]piperazine and 1-[3-(chloro)phenyl]piperazine are peripheral 5-HT agonists[5] and in addition have been shown to bind at central 5-HT sites.[6] Substituted phenylpiperazines were also found to possess antipsychotic activity.[7]

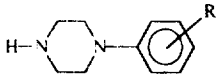
Prelog first reported the synthesis of 1-Arylpiperazines from bis(2-chloroethyl)amine hydrochloride by condensing it with substituted anilines in the presence of a base.[8,9] Moderate yields of 1-Arylpiperazines were reported by carrying out the reaction in diglyme,[10-12] alcohols,[7,13-15] and good yields in chlorobenzene.[16,17] A recent paper by Eyal Mishani, et al. reported the dry synthesis of Phenylpiperazines on alumina support in 40 mins.[18]

We report here an efficient and easy synthesis of 1-Arylpiperazines under MW irradiation. The reactants, being polar, effectively couple with microwaves. The short reaction time could be of immense importance in the production of potent neurological radiopharmaceuticals labeled with positron emitting isotopes suitable for Positron Emission Tomography (PET) study.[19]

General procedure: 0.61 g (6.6 mmol) of aniline, 0.79 g (4.4 mmol) of bis(2-chloroethyl)amine hydrochloride were taken in a round bottom flask and irradiated in the modified MW oven (KELVINATOR T-37, output 700 W) for 1 min. HCl gas evolved was trapped into NaOH solution kept outside the oven. The mixture was basified with NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and dried over sodium sulfate. $CHCl_3$ was distilled out and the resulting oil was subjected to column chromatography using silica gel of 60-120 mesh size to give pure 1-phenylpiperazine weighing 0.52 g (73% yield). Other piperazines (see table) were purified on silica gel column and characterized by their PMR spectral data.

Table

Optimized Yields of 1-Arylpiperazines under MW



R	Reaction Time (Mins.)	Isolated Yield (%)
H	1	73.2
3-Cl	2	57.2
4-Cl	2	47.2
2-CN	2	52.9
$3\text{-}CF_3$	1	55.8
$4\text{-}CH_3$	2	56.2
$4\text{-}COCH_3$	3	58.5

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