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An Efficient Scale up Process for Synthesis of N-Arylpiperazines

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ABSTRACT

An efficient protocol for the synthesis of various substituted phenylpiperazines was developed using sulfolane as solvent. The protocol was clean, high yielding and products were obtained in high purities (≥99%). It was also fast and convenient, as the final products were precipitated as hydrochloride salts and could be obtained by filtration. Sulfolane, an aprotic, dipolar, high boiling and recoverable solvent was used as a substitute for common organic solvents.

Keywords:

N-Arylpiperazines
Scale up
High purity
Sulfolane

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N-Arylpiperazines are an important class of organic compounds with prime importance in the field of medicinal chemistry.[1] These moieties are known to possess antihistaminic, antihypertensive, adrenolytic and anti inflammatory activities.[2] Arylpiperazines are also used in the field of neuroscience in particular, they are often found in ligands for serotonin (5-hydroxytryptamine, 5-HT)[3,4] dopamine receptors[5] and monoamine transporters.[6,7] Apart from their intrinsic biological activities N-arylpiperazines serve as vital building blocks for many drugs like aripiprazole, cariprazine, trazodone and nefazodone (Figure 1) and brepiprazole, an antipsychotic under development. Hence, there is an ongoing quest from the discovery and process chemists for their synthesis.

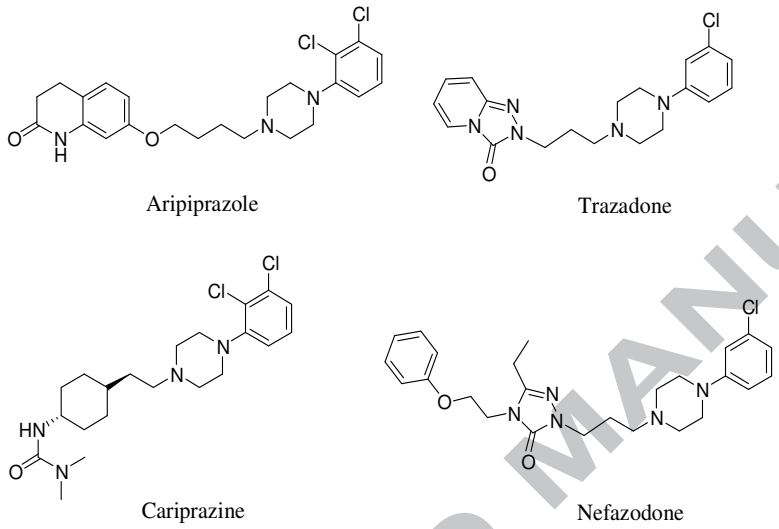


Figure 1. Some N-arylpiperazine based drugs

Interestingly the first report on the synthesis of N-arylpiperazines was by Prelog wherein aniline was condensed with N,N-bis(2-haloethyl)amine in presence of base.[8,9] During the last decade, the synthesis of N-arylpiperazines has witnessed enormous developments in terms of modifications of reaction conditions and evolution of newer approaches. Substitution of an aryl halide (SnAr) with unsubstituted piperazine facilitated by electron withdrawing group on the aromatic ring has been practiced for decades, while substitution of even unactivated halogen atoms by piperazines using a palladium catalyst [10] is a more recent development known as Buchwald[11] and Hartwig coupling.[12] The role of solvent is critical in this transformation, low boiling solvents are not preferred for this condensation, as products are obtained in low yields. Modifications involving the use of high boiling solvents at elevated temperatures in the presence of K2CO3 gave desired products in moderate yields. A few examples of solvents are 2-butoxyethanol (21% yield),[13] chlorobenzene (54% yield),[14] DMF (15% yield),[15] diglyme (76% yield)[16] and n-butanol (50-72% yield).[17,18] As these procedures involve extractions with an organic solvent and subsequent treatment with HCl gas to give the desired N-aryl piperazine salts, there is a need for developing alternatives where the use of an external base can be avoided to make them industrially viable. However, there are only a couple of reports[19,20] on the synthesis of N-arylpiperazines without base using xylene as solvent, PTSA as catalyst and ethanol for

recrystallization, where the time taken for reaction was 27-48 hours, yield was 82% and the product purity was not reported. Thus there was a need for the development of efficient protocols for the synthesis of N-arylpiperazine salts without use of external base in the reaction medium, avoiding solvent extraction and treatment with HCl gas. This would ultimately lead to increase in efficiency of the process and result in higher yields, giving rise to a scalable process. Herein we report an efficient procedure for synthesis of N-arylpiperazines using sulfolane[21] as high boiling solvent of reaction of anilines with bis(2-chloroethyl)amine hydrochloride to give N-arylpiperazine salts directly which can be isolated by simple filtration in excellent yields and high purity.

For the typical synthesis of N-arylpiperazine salts initially a few different solvents , polar, protic, aprotic and non-polar were tried to identify the best solvent for the conversion of 2,3-dichloroaniline to 1-(2,3-dichlorophenyl)piperazine hydrochloride . The tabulated results (Table 1) showed unambiguously that sulfolane was the one of choice.

Table 1.

Solvents used for reaction medium

Entry No	Solvent	Volumes	Temp°C	Reaction mass at 15 hrs		Product purity	Isolated yield
				1a %	3a %		
1	Isopropyl alcohol	10	80	55.9	1.7	--	--
2	1,2-Dichloro benzene	10	150	35.2	42.5	88	40
3	Glycerol	3	150	15.3	50.4	92	34
4	Diglyme	3	150	12.9	48.2	90.1	47
5	Ortho Xylene	10	140	12.6	50.2	67.6	50
6	Sulfolane	3	150	1.2	91.8	99.1	89

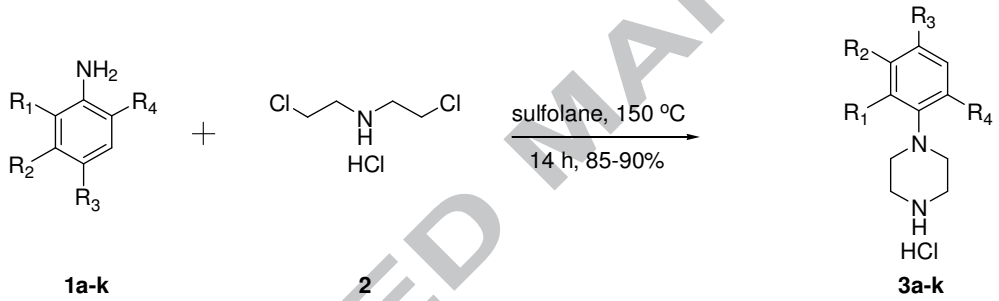
After selecting sulfolane as solvent for the reaction, different solvents were tried to precipitate the product from the reaction mixture. The yield and purity of isolated product with each solvent is mentioned below in (Table 2). The results showed that the acetone was the best solvent for isolation.

Table 2.

Solvents used for isolation

Entry No	Solvent	Yield	Purity%
1	Isopropyl alcohol	47	98.6
2	n-heptane	54	93.6
3	1,4-Dioxane	57	97.2
4	Methanol	64	98.8
5	Acetone	89	99.1

A typical preparation of a N-arylpiperazine is now described. The reaction of 2,3-dichloroaniline and bis(2-chloroethyl)amine hydrochloride in sulfolane was conducted at 150°C for 14 hours. Completion of the reaction was monitored by HPLC. The reaction mixture was cooled to about 45°C and diluted with acetone. Further cooling to 0°C resulted in the precipitation of a solid which was filtered and the precipitate was washed with chilled acetone to give the desired product 3a 1-(2,3-dichlorophenyl)piperazine hydrochloride, an intermediate for aripiprazole, in 89% yield. The product was characterized by 1H NMR, Mass and IR spectra and the data were matching well with the literature. The protocol was simple and clean and could be extended to many other arylpiperazines. The products were isolated with more than 99% purity. Since the prime aim was to have a scalable process, the synthesis of 3a was carried out at 1 kg level and executed without any difficulties. The filtrate in the 1 kg batch was distilled to recover acetone and sulfolane in good purity and yield. Having optimized the reaction conditions, we then wanted to generalize the protocol by screening different substrates to obtain various N-arylpiperazines which are incorporated in various drugs. Substitution was varied in the aniline ring and the process was found to work well, resulting in the formation of corresponding N-arylpiperazine hydrochlorides 3b-k in excellent yields (Table 3).



Scheme 1. Synthesis of N-arylpiperazine hydrochlorides in sulfolane

Table 3.

Synthesis of various N-arylpiperazine hydrochlorides 3a-k

Entry No	Substrate	Product	Yield (%)	Purity (%) by HPLC	Drug
1	R1,R2=Cl (1a)	R1,R2=Cl (3a)	89	99.21	Aripiprazole Cariprazine
2	R1=Cl (1b)	R1=Cl (3b)	90	99.88	Enpiprazole
3	R2=Cl (1c)	R2=Cl (3c)	91	99.27	Mepiprazole Nefazodone Trazodone Etoperidone
4	R3=Cl (1d)	R3=Cl (3d)	89	99.96	
5	R1=OH (1e)	R1=OH (3e)	87	99.09	Bifeprunox

6	R2=OH (1f)	R2=OH (3f)	85	99.74	
7	R3=OH (1g)	R3=OH (3g)	88	99.66	Posaconazole Itraconazole Ketoconazole Saperconazole
8	R1,R2,R3,R5=H (1h)	R1,R2,R3,R5=H (3h)	87	99.17	Levodropropizine Oxypertine Dropropizine
9	R3=F (1i)	R3=F (3i)	90	99.96	Niaprazine Monatepil
10	R2= Me, R4=Br (1j)	R2= Me, R4=Br (3j)	91	99.71	
11	R2=SO2Me (1k)	R2=SO2Me (3k)	92	99.74	

When aminophenols 1e-g were subjected to our process, phenylpiperazine salts 3e-g were obtained as hygroscopic solids which on washing with methanol/acetone (3:7) mixture formed free flowing powders. All the phenylpiperazines made in the study are used as intermediates for various drugs. The corresponding drugs are mentioned in table 3 in the last column.

We have thus demonstrated a high yielding, scalable protocol for synthesis of substituted phenylpiperazines using sulfolane, which has the following advantages.

Sulfolane is a versatile solvent and can be used for a wide range of synthesis. It is highly polar, has a high boiling point and has excellent chemical and thermal stability. It is completely miscible with water and hence kettles in which the reactions are performed can be readily cleaned with water. It is totally miscible with aromatic hydrocarbons and hence can be washed off from the precipitates by the later. It has very low skin penetration and high dipole moment. It is an aprotic (no acidic hydrogen atoms), recoverable and recyclable solvent. The procedure is clean and products are isolated by simple filtration as hydrochloride salts. It is applicable to various substituted anilines to give corresponding N-phenylpiperazine hydrochlorides (e.g. 3a-k) in excellent yields. All the products are found to be above 99% pure by HPLC.

We propose to extend our study to the use of recently published aprotic dipolar solvent, dihydrolevoglucosenone (cyrene) for piperazine formation.[22]

GENERAL PRECEDURE FOR SYNTHESIS OF 1-ARYLPIPERAZINE HYDROCHLORIDES

The following procedure for synthesis of 1-(2,3-dichlorophenyl)piperazine hydrochloride**(3a)** is illustrative.

A 20 liter round bottom flask connected to scrubber was charged with 2,3-dichloroaniline (1a) (1.0 kg, 6.17 mol) and bis(2-chloroethyl)amine hydrochloride(2) (1.43 kg, 8.02 mol) and

3.0 liters of sulfolane. The heterogeneous mixture was heated to 150°C to give a homogeneous solution which was stirred at 150°C for 14 hours, by which the time the reaction was completed as monitored by HPLC (see below Table 4). The reaction mixture was cooled to 45°C and diluted with 5.0 liters of acetone and further cooled to 0°C. The mixture was maintained at 0°C for 1 more hour to precipitate the desired product. This was filtered under nitrogen atmosphere and washed with 1 liter of chilled acetone and dried at 60°C under vacuum for 8 hours to yield 1-(2,3-dichlorophenyl)piperazine hydrochloride (3a) 1.47 kg (89%); Purity by HPLC: 99.21%; MP: 245-247°C; Mass: m/z 231.1 (M+, 35Cl); 1H NMR (400 MHz, DMSO-d6): 3.20 (s, 8H), 7.18 (dd, J =6.84, 2.76Hz, 1H), 7.32-7.36 (m, 2H), 9.50 (s, 2H) ppm; ^{13}C NMR (DMSO-d6) δ_C: 149.960, 132.650, 128.545, 126.110, 125.111, 119.730, 47.680 and 42.889; IR (KBr, γmax, cm-1): 3447(N-H), 2900(Ar C-H), 1254(C-N), 543(C-Cl).

The filtrate was charged to a 20 liter round bottom flask with distillation setup. The flask was heated upto100°C to distil out acetone at vapor temperature 50-52°C (85% recovery). The flask temperature was then raised to 150°C, and a vacuum of 15-10 mm of Hg applied to recover 93% of pure sulfolane (^{1}H NMR) at vapor temperature 100-103°C.

Table 4. Reaction mass analysis by HPLC

Time in Hrs	1-(2,3-dichlorophenyl) piperazine.HCl (Product)%	2,3-Dichloro aniline%
4	64.9	16.1
6	67.7	11.4
8	70.7	10.9
10	76.6	6.8
12	77.9	3.2
14	82.5	1.5

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Graphical abstract