Solventless microwave assisted protocol for synthesis of arylalkylpiperazines using Cs-base†

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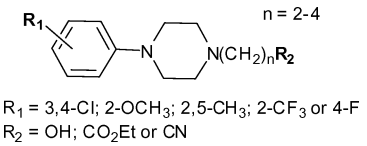
A series of some arylalkylpiperazines was prepared in good yields under microwave irradiation in dry media conditions using CsOH with high chemo- and regioselectivity.

Introduction

Synthesis of arylalkylpiperazines is obviously an important task in modern medicinal chemistry. Some of them constitute an essential part of a large number of biologically active compounds. For example, some derivatives, containing amidoalkyl or amidoaryl groups, possess central nervous system depressant activity, present excellent 5-HT_2 receptor antagonism and 5-HT_{1A} receptor agonism, or display D_2 and 5-HT_{1A} receptor affinity.[1]

The synthetic approaches to tertiary aliphatic amines from secondary amines include reductive amination[2] and direct *N*-alkylation.[3] The nucleophilic attack of alkyl halides by secondary amines in the presence of base is useful for the preparation of tertiary amines, but the reaction requires long reaction times and gives a mixture of secondary and tertiary amines. Furthermore, reaction times of *N*-alkylation of arylpiperazines with primary alkyl halides, which is an important synthetic method to obtain the corresponding arylalkylpiperazines, range between 4 and 26 h.[4] In recent years, microwave irradiation has become popular among synthetic organic chemists both to improve classical organic reactions, shortening reaction times and/or improving yields, as well as promoting new reactions.[5] Moreover, when carrying out a reaction in a microwave oven, the use of a solvent can be avoided, allowing eco-friendly synthesis and offering several advantages, such as to reduce the risk of explosion and easier work-up.[6]

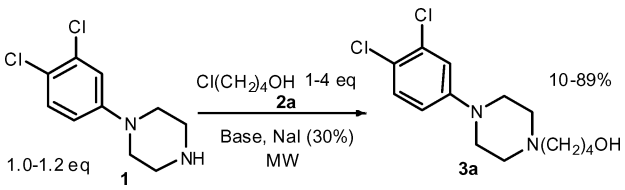
As a part of our program directed toward the preparation of new derivatives with potential CNS activities,[7] we developed a method to synthesize arylalkylpiperazine moieties as synthetic intermediates involving an eco-friendly method for the chemoselective preparation of tertiary amine corresponding to alkylsubstituted arylpiperazines (Scheme 1).



Scheme 1

Results and discussion

We initially studied the microwave-assisted coupling of 3,4-(dichlorophenyl)piperazine **1** with 4-chlorobutanol **2a** using a solventless procedure (Scheme 2).



Scheme 2

The first attempts to prepare **3a** using **1** in slight excess (1.2 eq) to reduce overalkylations with **2a** (1 eq) were unsuccessful (10–19%). The reactants were adsorbed on the surface of the additive (Al_2O_3/base in 4:1 ratio) in large excess and a base, such as $NaHCO_3$, K_2CO_3 or KOH, was employed. As expected, direct *N*-monoalkylation techniques using bases like $NaHCO_3$ or K_2CO_3 and a large excess of **2a** (2 eq) gave, after optimization, moderate yields (40 and 48%, respectively) because of overalkylations. The volatility of **2a** and the basic properties of **1** in the reaction mixture can induce a lower yield. In the last few years, Cs-base promoted synthetic protocols have been widely applied to the formation of a variety of carbon-hetero atom bond forming reactions.[8–10] Recently, an elegant methodology for direct amination reactions promoted by $CsOH{\cdot}H_2O$ with the use of DMF has been reported.[8] However, this report is limited to alkylation of primary alkyl amines which can be rapidly converted to the secondary amine under the classical heating method in moderate to good yields. With the aim of efficiently synthesizing substituted arylpiperazines, S_N2 alkylation using monohydrate CsOH or $Cs(CO_3)_2$ as base under microwave irradiation was investigated (Scheme 2, Table 1).

We demonstrate that arylalkylpiperazine **3a** can be obtained in good yield, using a Cs-base as base under microwave irradiation without solvent. These conditions reaction exhibited enhanced chemoselectivities in amine alkylation compared to the previously reported protocols. The multimode reactor used was an ETHOS Synth Lab station (Ethos start, Milestone Inc.).

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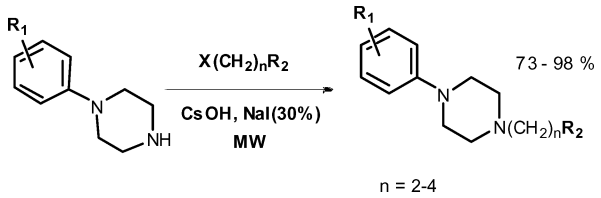
Table 1 Solventless *N*-alkylation under microwave irradiation

Entry[a]	Base (eq)	Reaction conditions	Yield[b] (**3a**)
1	$CsOH{\cdot}H_2O$ (1 eq)	200 W; 50 °C; 2 × 15 min[d]	64%
2	Cs_2CO_3 (1.2 eq)	150 W; 50 °C; 30 min	63%
3	$CsOH{\cdot}H_2O$ (2 eq)	200 W; 50 °C; 2 × 15 min[d]	79%
4	CsOH (2 eq)[c]	200 W; 50 °C; 3 × 15 min[d]	89%

[a] All the reactions are performed using amine **1** (1 eq: 4 mmol) with haloalkane **2a** (4 eq) in the presence of 30% NaI and 0.8 g of dessicant ($MgSO_4$). [b] % Yield relative to amine **1**. [c] $CsOH{\cdot}H_2O$ was dried at 120 °C for 24h. [d] Pulse irradiation (with 90 s intervals).

90 s intervals were needed between pulse irradiation because the sensitivity of the products to heating. Furthermore, monohydrate CsOH (Table 1, entry 1 and 3) was found to be superior. Cesium bicarbonate (Table 1, entry 2) gave lower conversions, presumably due to decreased basicity and solubility. However, when CsOH is strictly dried, the yield increased to 89%. Moreover, NaI is used to facilitate the reaction by a halogen exchange activation. This methodology exhibits several advantages over the conventional heating by reducing the reaction time, improving the reaction yield and also by eliminating the side reactions. With this general procedure for the synthesis of **3a** (Table 1, entry 4) in hand, we then investigated direct *N*-monoalkylation using a variety of arylpiperazines and haloalkanes (Table 2, Scheme 3). In order to apply this new procedure to a series of arylpiperazines with various haloalkanes, we have modified some parameters, such as the power of the microwave oven, reaction time, temperature and quantity of haloalkane (3–5 eq), due to the physico-chemical properties of the used haloalkane. After monitoring by TLC, the optimized yields are reported in Table 2. For the haloalkanes **2c** and **2d**, the optimization seems to be haloalkane-dependent whatever amine is used.

As shown in Table 2, various functionalized primary chloro or bromoalkane derivatives were efficiently coupled with various arylpiperazines generating the corresponding tertiary amines. This methodology can be applied with alcohol, ester or nitrile



Scheme 3

derivatives. As expected, the reactions still exhibited high yields. In order to show the advantage of the use of a microwave reactor, we realized the preparation of compound **5b** under the same experimental conditions without microwave irradiation but using an oil bath for heating instead. Only 21% yield of compound **5b** was isolated after 18 h *versus* 96% yield after 4 × 20 min, under microwave irradiation. Mono-*N*-alkylation was then applicable with the use of a range of different arylpiperazines, offering similar trends. In all entries (Table 2), very little or no overalkylation was detected. This chemoselectivity can be explain by analogy with the mechanism proposed by K. W. Jung and coworkers,[10] a strong affinity of the tertiary amine for the cesium cation reduces the nucleophilicity of the tertiary amine and produce a sterically hindered complex.

Conclusion

In order to obtain antipsychotic precursors, we developed a synthetic method of arylalkylpiperazines under microwave irradiation in "dry" media conditions including Cs(OH) as base to promote chemo- and regioselectively the *N*-alkylation. Thanks to this approach, substituted arylpiperazine derivatives of pharmacological interest were obtained in good yields. This simple and convenient methodology corresponds to a "green chemistry" approach which has been widely adopted to meet the fundamental scientific challenges of protecting human health and the environment. Currently, efforts are underway to extend this procedure to the synthesis of cyclic tertiary amines from primary amines by di-*N*-alkylation.

Table 2 CsOH-promoted *N*-alkylation using various secondary amines and haloalkanes

			$X(CH_2)_nR_2$				
Amine (quantity)	R_1	Haloalkane (equivalent)	X	*n*	R_2	Reaction conditions	Yield[a] (product)[b]
1 (4 mmol)	3,4-Cl	**2a** (4 eq)	Cl	4	OH	200 W; 60 °C; 3 × 15 min[c]	89% (**3a**)
4 (4 mmol)	2-OCH_3	**2a** (4 eq)	Cl	4	OH	150 W; 55 °C; 4 × 15 min[c]	90% (**5a**)
6 (2 mmol)	4-F	**2a** (4 eq)	Cl	4	OH	200 W; 60 °C; 3 min	95% (**7a**)
1 (2 mmol)	3,4-Cl	**2b** (3 eq)	Cl	3	CN	200 W; 60 °C; 9 min	90% (**3b**)
4 (4 mmol)	2-OCH_3	**2b** (3 eq)	Cl	3	CN	150 W; 60 °C; 4 × 20 min[c]	96% (**5b**)
6 (2 mmol)	4-F	**2b** (3 eq)	Cl	3	CN	200 W; 60 °C; 5 min	86% (**7b**)
8 (4 mmol)	2,5-CH_3	**2b** (3 eq)	Cl	3	CN	200 W; 60 °C; 3 × 15 min[c]	73% (**9b**)
1 (2 mmol)	3,4-Cl	**2c** (5 eq)[d]	Br	2	CN	100 W; 50 °C; 4 × 5 min[c]	82% (**3c**)
6 (2 mmol)	4-F	**2c** (5 eq)[d]	Br	2	CN	100 W; 50 °C; 4 × 5 min[c]	88% (**7c**)
8 (2 mmol)	2,5-CH_3	**2c** (5 eq)[d]	Br	2	CN	100 W; 50 °C; 4 × 5 min[c]	74% (**9c**)
10 (2 mmol)	3-$CF_3{\cdot}$HCl	**2c** (5 eq)[d]	Br	2	CN	100 W; 50 °C; 4 × 5 min[c]	86% (**11c**)
1 (2 mmol)	3,4-Cl	**2d** (3 eq)	Cl	3	CO_2Et	150 W; 50 °C; 4 × 4 min[c]	98% (**3d**)
6 (2 mmol)	4-F	**2d** (3 eq)	Cl	3	CO_2Et	150 W; 50 °C; 4 × 4 min[c]	95% (**7d**)
8 (2 mmol)	2,5-CH_3	**2d** (3 eq)	Cl	3	CO_2Et	150 W; 50 °C; 4 × 4 min[c]	97% (**9d**)
10 (2 mmol)	3-$CF_3{\cdot}$HCl	**2d** (3 eq)	Cl	3	CO_2Et	150 W; 50 °C; 4 × 4 min[c]	97% (**11d**)

[a] All the reactions are performed using 1 equivalent of arylpiperazine with corresponding haloalkane in the presence of 30% NaI and 0.8 g of dessicant ($MgSO_4$), promoted by dried CsOH. [b] NMR and mass spectra of all synthesized products are in accordance with the literature.[11] [c] Pulse irradiation (with 90 s intervals). [d] No NaI was added in the reaction mixture containing bromohaloalkane **2c**.

Experimental

General procedure

To a mixture of arylpiperazine (1 eq), sodium iodide (0.3 eq), magnesium sulfate (0.8 g) and cesium hydroxide (2 eq) was added 4-haloalkane (3–5 eq). The reaction mixture was stirred and irradiated in a microwave oven (Ethos start) for an appropriate time and temperature. After being cooled down, the mixture was then taken up in 1 N NaOH and then extracted with AcOEt (3 × 30 mL). The organic layers were washed with water (2 × 30 mL), with brine (30 mL) and dried over anhydrous sodium sulfate. Concentration of the solvent under reduced pressure and drying in a oven under reduced pressure afforded the desired alkylarylpiperazine.

For the reactions carried out with 4-chorobutanol **2a**, the corresponding desired product was isolated and separated to secondary products by chromatographic column with AcOEt/*n*-hexane as eluent. For example: 4-[4-(3,4-dichlorophenyl)piperazin-1-yl]butan-1-ol **3a** NMR ^{1}H (200 MHz, $CDCl_3$) 7.26 (d, J = 9.0 Hz, 1H), 6.95 (d, J = 2.9 Hz, 1H), 6.69–6.75 (dd, J = 9.0 and 2.8 Hz, 1H), 3.64–3.56 (m, 2H), 3.47–3.41 (m, 1H), 3.27–3.22 (m, 4H), 2.74–2.69 (m, 4H), 2.50–2.55 (m, 2H), 1.72–1.63 (m, 4H); NMR ^{13}C (50 MHz, $CDCl_3$) 150.7, 132.7, 130.4, 122.0, 117.1, 115.2, 70.6, 58.3, 52.8, 48.6, 27.7, 23.6; HRMS (EI): calc. for $C_{14}H_{20}N_2OCl_2$ (M^+) 303.1025, found 303.1023.

Acknowledgements

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