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Solvent-free microwave-assisted synthesis of aripiprazole

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ABSTRACT

Aripiprazole is a widely used antipsychotic approved by the FDA (Food and Drug Administration) in 2002. Methods for preparation of aripiprazole mainly involve the use of expensive and toxic solvents, and the reaction time can be even several hours long. Our method allows to obtain aripiprazole with a yield of approximately 70–80% over just a few minutes using solvent-free conditions in the presence of PTC (Phase Transfer Catalysts) and microwave radiation.

1. Introduction

The antipsychotic efficacy of aripiprazole (**1**) is due to its activity as a partial agonist of dopamine D_2 and serotonin 5-HT_{1A} receptors, and antagonist of a 5-HT_{2A} serotonin receptor (**Fig. 1**). Aripiprazole (**1**) is recommended for the treatment of schizophrenia and manic episodes.

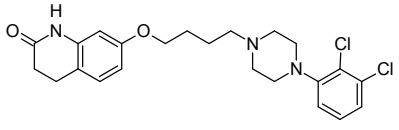

Fig. 1. Structure of aripiprazole (**1**)

The most widely described in the literature synthetic route of aripiprazole (**1**) is a reaction between 7-(4-halobutoxy)-3,4-dihydrocarbostyril (BBQ) and 1-(2,3-dichlorophenyl)piperazine (DCP) in the presence of bases, such as triethylamine,[1-3] pyridine, sodium hydroxide or hydride,[1,4] potassium,[1,4-13] carbonate or bicarbonate,[15] sodium, [1,8,14-15] and caesium.[15] in solvents such as acetonitrile,[1-3,6,11,14

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DMF,[7,10,12,15] DMSO, dioxane, THF, benzene, toluene, xylene,[1] water,[5-4,9] or alcohols, such as methanol,[8] ethanol,[13,16] isopropanol or *n*-butanol.[6] Catalytic amounts of potassium iodide[1] or sodium iodide[1,10,12] introduced to the reaction mixture can increase the reaction rate.

According to the data reported in the literature, the temperature range for the reaction can vary from 20 to 200 °C, with the optimum temperature ranging from 60 to 120 °C. In such conditions, the reaction time is from a few to 24 hours. Methods of aripiprazole (**1**) synthesis utilising PTC (Phase Transfer Catalysis) catalysts are also known, e.g. TBAB (tetrabutylammonium bromide),[6,14] sodium dodecyl sulphate, hexadecyltrimethylammonium bromide, sodium lauryl sulphate.[6]

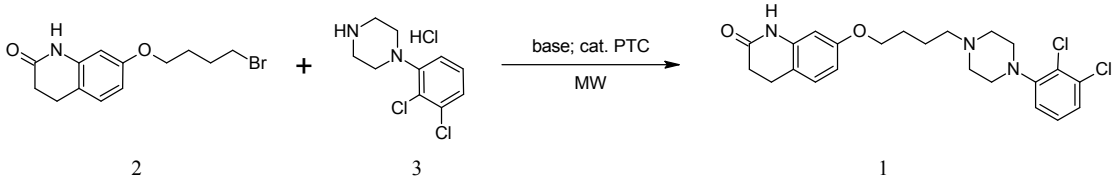
The majority of known methods for aripiprazole synthesis require the use of solvents often being toxic, non-environmentally friendly, and non-cost effective. Furthermore, the time span of aripiprazole (**1**) synthesis according to the known methods may exceed tens of hours.

Also known is a microwave synthesis method[17] for aripiprazole (**1**), which reduces the synthesis time to as short as 2 minutes. However, this method calls for using a toxic and expensive solvent, i.e. acetonitrile.

Currently, there is no literature data available about a method of aripiprazole (**1**) synthesis under solvent-free conditions. The long-term research involvement of our laboratory in the synthesis of ligands belonging the group of long-chain arylpiperazines, including aripiprazole (**1**),[18-21] enriched our experience in both a conventional synthesis under solvent-free conditions, e.g. imide *N*-alkylation,[22] and a ligand synthesis under microwave irradiation.[23]

2. Results and Discussion

The research aimed to select the optimal conditions for aripiprazole (**1**) synthesis involving reaction between 7-(4-bromobutoxy)-3,4-dihydrocarbostyril (**2**) and 1-(2,3-dichlorophenyl)piperazine (**3**) (**Fig. 2**) under microwave irradiation, and in the presence of a phase transfer catalyst (PTC). The progress of the reaction was evaluated by TLC after 60 seconds of reaction. If unreacted starting materials were observed in the reaction mixture, the reaction was continued for further 60 seconds.

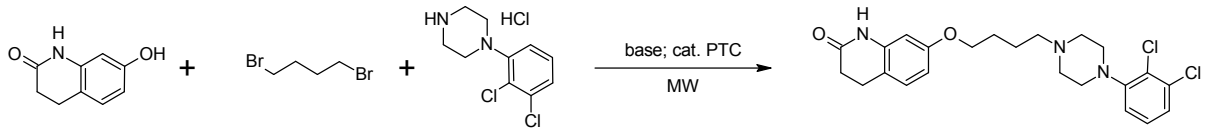


2 3 1

Fig. 2. Synthesis of aripiprazole (**1**)

The effects of changing the base (and its amount), the solvent (and its amount), the phase transfer catalyst, as well as the microwave power applied on the yield were evaluated.

The feasibility of a one-pot synthesis method was also assessed. In the said method, aripiprazole (**1**) is obtained from 7-hydroxy-3,4-dihydro-2(1H)-quinolinone (**4**), 1,4-dibromobutane (**5**), and 1-(2,3-dichlorophenyl)piperazine (**3**) without isolation of the intermediates (**Fig. 3**). Table 1 summarises the results of all the reactions. Two different reaction variants were used: simultaneous addition of all reagents (**Table 1**, **entry 15**), and a step-wise procedure, in which reagents (**4**) and (**5**) were reacted under microwave irradiation for 120 seconds, and the reaction was continued for additional 120 seconds following addition of another reagent (**3**) (**Table 1**, **entry 16**).



4 5 3 1

Fig. 3. One-pot synthesis of aripiprazole (**1**)

Table. 1. The yield of aripiprazole (**1**) synthesis

Entry	Conditions						Time [s]		Yield [%]	
	Substrate	Base / Eq		PTC	Solvent / [% mass]		MW 50 [W]	MW 100 [W]	MW 50 [W]	MW 100 [W]
1	**2**	K_2CO_3	3	TBAB	-	0	360	360	0	2
2*							60	60	0	61
3*							180	180	81	70
4					DMF	2	120	120	3	38
5						10	120	120	79	78
6						20	120	120	60	51
7			1			10	120	120	51	55
8			1.5			10	120	120	48	45
9			3		H_2O	10	120	120	60	73
10					ACN	10	60	60	60	67
11				TEAC	DMF	10	60	60	64	76
12				DABCO		10	60	60	50	44
13		NaOH	3	TBAB		10	60	60	67	55
14		TEA				10	120	90	48	46
15**	**4**	K_2CO_3				10	120	120	18	45
16***						10	240	240	38	10

* powdered mixture was compacted into a dense pile using a glass baguette; BBQ = 7-(4-bromobutoxy)-3,4-dihydrocarbostyril; 7-OHQ = 7-hydroxy-3,4-dihydro-2(1H)-quinolinone; Base / Eq = equivalent of the base calculated versus the amount of the substrate (BBQ or 7-OHQ); TEA = triethylamine; TBAB = tetra-n-butylammonium bromide, TEAC = tetraethylammonium chloride, DABCO = 1,4-diazabicyclo[2.2.2]octane; PTC = Phase-transfer catalyst; DMF = dimethylformamide; ACN = acetonitrile; MW 50/100 [W] = microwave irradiation power.

** one-step procedure, in which all reagents (**3**), (**4**) and (**5**) were reacted under microwave irradiation for 120 seconds

*** step-wise procedure, in which reagents (**4**) and (**5**) were reacted under microwave irradiation for 120 seconds, and the reaction was continued for additional 120 seconds following addition of another reagent (**3**)

A three-fold molar excess of K_2CO_3 used as a base resulted in higher reaction yield. Moreover, K_2CO_3 is a safer-to-use base than the other tested. The addition of TBAB or TEAC as a phase transfer catalyst provided satisfactory results as well. All the tested solvents proved to be feasible for the described method, yet their mass fraction in the reaction mixture is of an uttermost importance. The best results were obtained using 10% by mass DMF. In the absence of solvent conversion rate was close to zero. Compaction of a powdered mixture into a dense pile with a glass baguette provided a significant gain in the reaction yield (**Table 1**, **entries 1-2**). The solvent-free conditions with irradiation at 50 W (**Table 1**, **entry 3**) have proven to be the optimal reaction method (the highest yield was obtained). Notably, using water as a solvent also resulted in high reaction yields (**Table 1, entry 9**). The microwave power applied also significantly influenced the reaction yield. A rise in the reaction yield with an increase of the microwave power used would be an intuitive observation, however this was not true for some of the syntheses. Too strong microwave powers applied lead to a partial break-down of the reaction mixture, which in turn decreases the final yield. The decrease in the yield may also be attributed to the decrease in selectivity as the temperature in the reaction medium rises.

Interestingly, the tested one-pot method resulted in approximately 40% yields for both the tested reaction variants. However, reacting all the substances at once (**Table 1**, **entry 15**) required higher microwave powers (100 W), while in the other procedure (**Table 1**, **entry 16**) (with a step-wise addition of reagents) irradiation with 50 W power only provided better results.

3. Conclusions

As described herein, aripiprazole (**1**), a known antidepressant, has been obtained in a solvent-free reaction enhanced by a microwave radiation. This procedure was found to be both time- and cost-effective, as well as safe for the environment thanks to the shortened reaction time and the limited use of toxic solvents. The use of 3 equivalents of K_2CO_3 as a base, 0.1 equivalents of TBAB (Phase Transfer Catalyst), and irradiation at 100 W microwave power were found to be the best conditions for aripiprazole (**1**) synthesis, with a yield of the desired product amounting to 81%. Advantageously, this procedure allows for a total elimination of any solvents. Comparative results for syntheses with the addition of DMF, ACN or water show that aripiprazole is also formed, but the final product contains a greater amount of impurities. DMF can be replaced with more environmentally-friendly solvent, i.e., water, without a significant impact on the results, however the benefits of a solvent-free synthesis still prevail. In the one-pot reaction, aripiprazole was obtained with a lower yield (44%), but according to this method synthesis could be done as a one-step procedure only. Our additional studies have also proved that the described aripiprazole synthesis, after appropriate optimization, can be used in the synthesis of other long chain arylpiperazines.

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4. Experimental

4.1. Materials and Methods

Reactants were purchased from Sigma Aldrich, and solvents used in the synthesis and purification steps were purchased from POCh. Analytical thin-layer chromatography (TLC) using 9:1 chloroform:methanol mixture was performed on silica gel on aluminium foil (Sigma Aldrich) with a 254 nm fluorescent dye (layer thickness: 200 μm, pore diameter: 60 Å, particle size: 8.0–12.0 μm) and a UV light source at 254 nm was used for the analysis. For HPLC analysis, Perkin Elmer Series 200 HPLC apparatus with a XTerra RP C-18 (particle size: 3.5 μm, 4.6x150 mm) column and elution with

1:1 MeOH:H_2O mixture acidified with 0.1% formic acid as a mobile phase were used. ^{1}H NMR spectra were recorded with Bruker Avance 300 MHz with TMS as an internal reference. Melting point was measured using Böetius apparatus. FT-IR spectra were recorded on Thermo Scientific Nicolet iS5 FT-IR Spectrometer.

4.2. General synthetic procedure

*BBQ (**2**) as the starting material*

A mixture of 3.35 mmol (1.00 g) 7-(4-bromobuthoxy)-3,4-dihydrocarbostyril (BBQ) (**2**), 3.70 mmol (0.99 g) 1-(2,3-dichlorophenyl)piperazine hydrochloride (DCP) (**3**), and different bases, such as 10/5/3.33 mmol (1.39/0.69/0.46 g) K_2CO_3 or 10 mmol (0.4 g) NaOH or 10 mmol (1.33 cm^3) TEA, and 0.3 mmol PTC, such as TBAB (0.1 g)/TEAC (0.05 g)/DABCO (0.05 g), was prepared using a mortar. The mixture was transferred to a round bottom flask and 20/10/2 % by mass (0.92/0.41/0.08 cm^3) DMF or 10 % by mass (0.5/0.39 cm^3) ACN/H_2O was added, or the substrates were reacted under solvent-free conditions. Reaction mixture was stirred to distribute the solvent in the entire volume of the mixture, and in the case of solvent-free reaction, the powdered mixture was compacted into a dense pile with a glass baguette. Subsequently, the reaction mixture was placed in a CEM Discovery microwave reactor and irradiated with microwaves at either 50 or 100 W. The reaction mixture was irradiated at 30-second intervals until complete conversion of the substrates, as monitored by a thin layer chromatography (TLC).

*7OHQ (**4**) as the starting material (one-pot procedure)*

For the one-pot procedure involving a single-step reaction, the mixture of 6.13 mmol (1.00 g) 7-hydroxy-3,4-dihydro-2(1H)-quinolinone (7-OHQ) (**4**), 5.23 mmol (1.4 g) 1-(2,3-dichlorophenyl)piperazine hydrochloride (DCP) (**3**), and 18.38 mmol (2.54 g) K_2CO_3 and 0.6 mmol (0.2 g) TBAB was ground in a mortar. The entire mixture was then transferred to a round bottom flask and 5.86 mmol (0.7 cm^3) of 1,4-dibromobutane (**5**) and 10% by mass (0.73 cm^3) DMF was added. The reaction mixture was heated in a CEM Discovery microwave reactor under reflux with irradiation with microwaves at either 50 or 100 W.

For a two-step one-pot reaction, the reaction mixture was prepared as described previously, except that 5.23 mmol (1.4 g) of 1-(2,3-dichlorophenyl)-piperazine hydrochloride (DCP) (**3**) was introduced to the mixture after a 120-second irradiation with microwaves at 50 or 100 W. In either case, the reaction progress was monitored by a thin layer chromatography (TLC).

Isolation of products

To isolate the final product obtained in each instance, the reaction mixture was transferred to a beaker containing 50 cm^3 of water. Inorganic salts were dissolved, aripiprazole was filtered off, washed with water and air-dried. Crude aripiprazole precipitate was purified by crystallisation from isopropanol.

4.3 Physical and Spectral Data

7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1H)-one (1)

Yield 81%, white solid, m.p. 139°C (isopropanol), R_f: 0.49. RT (min.): 7.43. FT-IR, ν, cm^{-1}, 3325 (N-H stretch), 3108 (aromatic C-H stretch), 2946 (aliphatic C-H stretch), 1678 (C=O stretch), 1594-1445 (aromatic region), 1174 (C-N stretch), 773 (C-Cl stretch). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.21 – 7.13 (m, 2H), 7.07 (d, J = 8.3 Hz, 1H), 7.02 – 6.95 (m, 1H), 6.55 (dd, J = 8.3, 2.4 Hz, 1H), 6.35 (d, J = 2.4 Hz, 1H), 3.99 (t, J = 6.0 Hz, 2H), 3.14 (broad s, 4H), 2.92 (t, J = 7.5 Hz, 2H), 2.74 (broad s, 4H), 2.64 (dd, J = 8.4, 6.6 Hz, 2H), 2.60 – 2.53 (m, 2H), 1.88-1.72 (m, 4H).

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